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(54) **Omega-cycloalkyl-prostaglandin E2 derivatives**

Omega-Zykloalkyl-Prostaglandin E2 Derivate

Dérivés omega-cycloalkyl-prostaglandine E2

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(73) Proprietor: **ONO PHARMACEUTICAL CO., LTD.**
Chuo-ku Osaka 541 (JP)

(72) Inventors:
- **Tani, Kousuke, c/o Minase Research Inst.**
Mishima-gun, Osaka (JP)
- **Ohuchida, Shuichi, c/o Minase Research Inst.**
Mishima-gun, Osaka (JP)

(74) Representative: **Bentham, Stephen et al**
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

(56) References cited:
US-A- 4 132 738
US-A- 4 336 404
US-A- 4 363 817

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Description

Field of Invention

[0001] This invention relates to ω-cycloalkyl-prostaglandin E_2 derivatives, processes for their preparation and pharmaceutical compositions containing them.

Background

[0002] Prostaglandin E_2 (abbreviated as PGE_2 hereafter) has been known as metabolite in the arachidonate cascade. It has been known that PGE_2 has cyto-protective activity, uterine contractile activity, a pain-inducing effect, a promoting effect of digestive peristalsis, an awaking effect, a suppressive effect of gastric acid secretion, hypotensive activity and diuretic activity etc.

[0003] In recent study, it was found that PGE_2 receptor was divided into some subtype which possess different physiological role each other. At present, four receptor subtype are known and they are called as EP_1, EP_2, EP_3 and EP_4 (Negishi M. et al, J. Lipid Mediators Cell Signaling, 12, 379-391 (1995)).

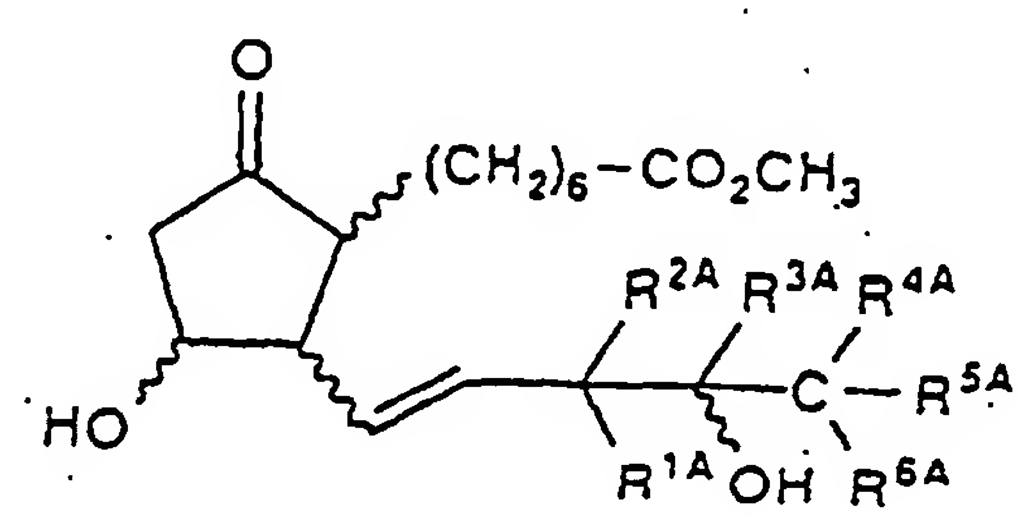
[0004] The present inventors investigated to find new compounds which bind on each receptors specifically, we found that the compounds of present invention could bind strongly on EP_2 subtype receptor and achieved the present invention.

[0005] The compounds of formula (I) of the present invention, as hereinafter defined, possess a binding activity for EP_2 subtype receptor strongly. Therefore, they are useful for prevention and/or treatment of immunological diseases (autoimmune diseases, organ transplantation, etc.), asthma, osteodystrophy, neuronal cell death, hepatopathy, abortion, premature birth or retina neuropathy of glaucoma etc.

[0006] Among the compounds of the present invention of the formula (I), compounds which bind weakly on receptor subtypes except for EP_2 and other arachidonic acid metabolism receptors (thromboxane receptor, PGI_2 receptor, etc.) do not express other effects and therefore, it is thought that such compounds will be a medical agent which have less side-effects.

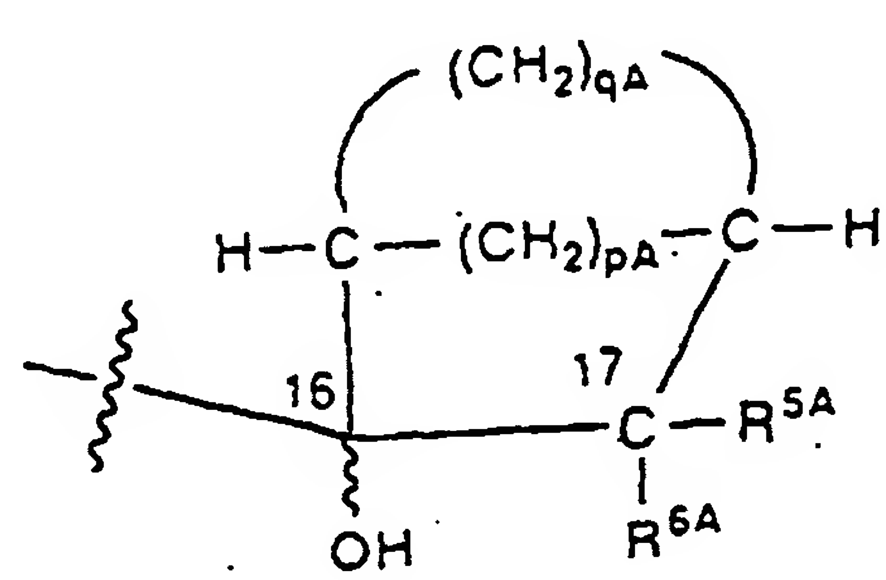
[0007] On the other hand, many patent applications of PG derivatives were known. The following applications are mentioned for example.

[0008] In the specification of United State Patent No. 4132738, a compound of the formula (A)

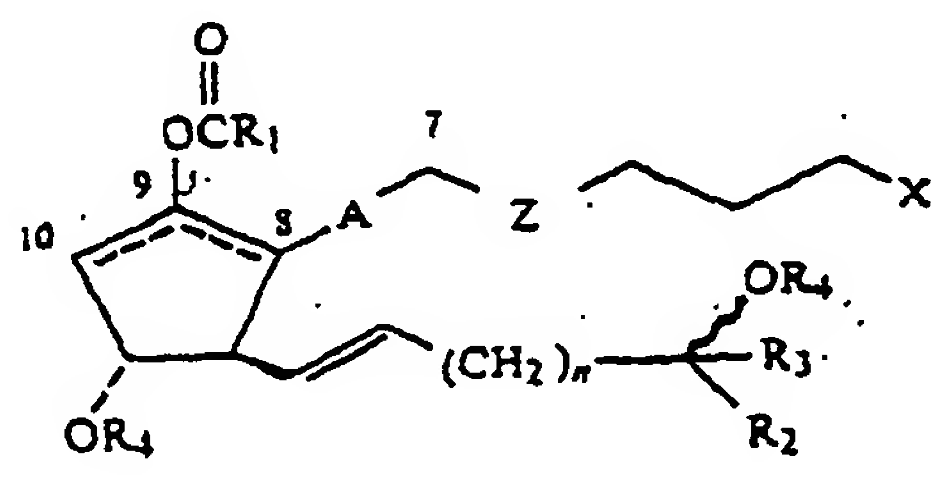


(A)

wherein R^{1A} and R^{2A} is hydrogen atom;
R^{3A} is hydrogen atom, or together with R^{4A} is a methylene chain of 4 carbon atoms such that a cycloalkyl of 6 carbon atoms inclusive is formed, or together with R^{4A} is a bicycloalkenyl or bicycloalkyl moiety having the formula



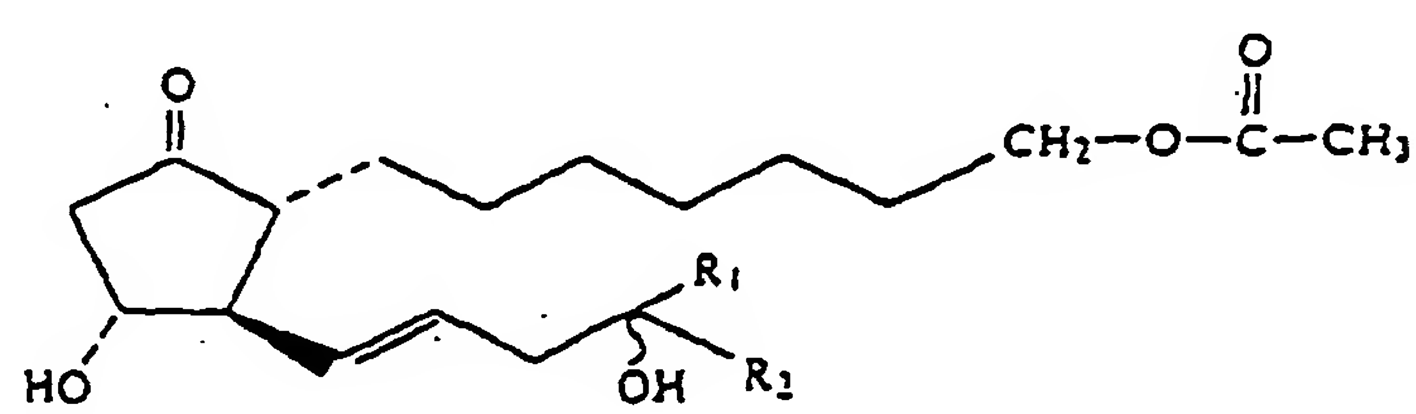
(in which pA is an integer having a value of from 0 to 1 and qA is an integer having a value of from 2 to 3 and wherein the double bond of such bicycloalkenyl is in the qA bridge);
R^{4A} together with R^{3A} forms a cycloalkyl or bicylcloalkyl or bicycloalkenyl as defined above, or together with R^{5A} is a methylene chain of 3 carbon atoms such that a cycloalkyl of 4 carbon atoms inclusive is formed;
R^{5A} is hydrogen atom, or together with R^{4A} forms a cycloalkyl as defined above; and
R^{6A} is hydrogen atom or straight-chain alkyl having from 1 to 8 carbon atoms; are disclosed as having an inhibitory activity on prostaglandin like.
In USP No. 4,363,817, the prostaglandin C-9 enol acylate analogs of formula



wherein:

the dashed line in the cyclopentyl ring represents the presence of a double carbon-carbon bond at either C_8-C_9 or C_9-C_{10}; Z is cis vinylene or ethylene; n is 0 or 1; A represents the presence of a single carbon-carbon bond between C_7 and C_8 which is in the α-configuration when there is a double carbon-carbon bond between C_7 and C_{10} and is in a plane of the 5 membered ring when there is a double carbon-carbon bond between C_8 and C_9; X is CH_2OH, CH_2OCOCH_3, CO_2M where M is H+, Na+, K+, ½Ca++, $NH{+}_3C(C_2H_5OH)$, CH_3, C_2H_5 or another pharmacologically acceptable salt cation or ester or $CONHR_4$; R_1 is n-alkyl of 1 to 20 carbon atoms which is optionally substituted with 0, N or S, cyclic alkyl of 3 to 12 carbon atoms optionally substituted with O, N or S, bicyclic alkyl of 7 to 12 carbon atoms, aryl of 6 to 12 carbon atoms optionally substituted with an n-alkyl group of 1 to 10 carbon atoms or one or more halogen atoms, alkenyl (Z and/or E) of 2 to 12 carbon atoms, alkenyl alkyl of 3 to 12 carbon atoms or O-n-alkyl of 1 to 20 carbon atoms wherein all of the above are optionally substituted with CO_2M, $CONHR_4$ or acetate; R_2 is H, n-alkyl of 1 to 10 carbon atoms, branched alkyl of 3 to 10 carbon atoms, cyclic alkyl of 3 to 10 carbon atoms optionally substituted with n-alkyl of 1 to 10 carbon atoms, bicyclic alkyl of 7 to 12 carbon atoms, aryl of 6 to 12 carbon atoms optionally substituted with n-alkyl of 1 to 10 carbon atoms, halogen, O, N or S; R_3 is a moiety coming within the definition of R_2 except that R_3 is not H; and R_4 is H or a moiety coming within the definition of COR_1,
are disclosed as prodrugs of the prostaglandin E_1 and E_2 class.

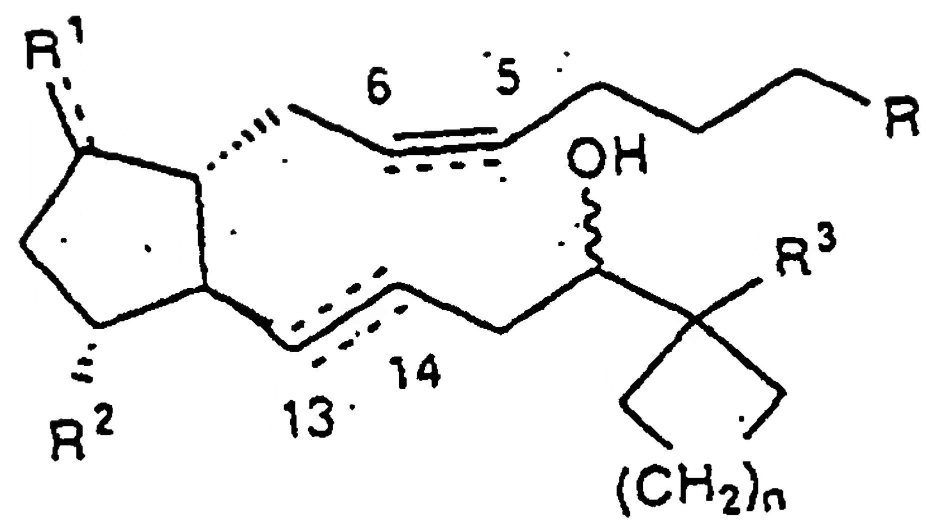
Further, in USP No. 4,336,404, 1-acyloxy-15-deoxy-16-hydroxy prostaglandin E_1 analogs of formula



wherein R_1 is H or methyl and R_2 is $C(CH_3)_2(CH_2)_2CH_3$ or $(CH_2)_3CH_3$ provided that when R_1 is methyl, R_2 is $(CH_2)_3CH_3$ and when R_1 is H, R_2 is $C(CH_3)_2(CH_2)_2CH_3$,
are disclosed as inhibitors of gastric secretion and as bronchodilators.

Disclosure of the Invention

[0009] The present invention accordingly provides (1) an ω-cycloalkyl-prostaglandin E_2 derivative of formula (I)



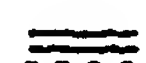
(I)

wherein R is carboxy or hydroxymethyl;
R^1 is oxo, methylene orhalogen atom,
R^2 is hydrogen atom, hydroxy or C1-4 alkoxy,
R^3 is hydrogen atom C1-8 alkyl, C2-8 alkenyl C2-8 alkynyl o- C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from (1)-(5):

(1) halogen atom,
(2) C1-4 alkoxy,
(3) C3-7 cycloalkyl,
(4) phenyl, and
(5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro and trifluoromethyl;

n is 0-4;

is single bond or double bond;

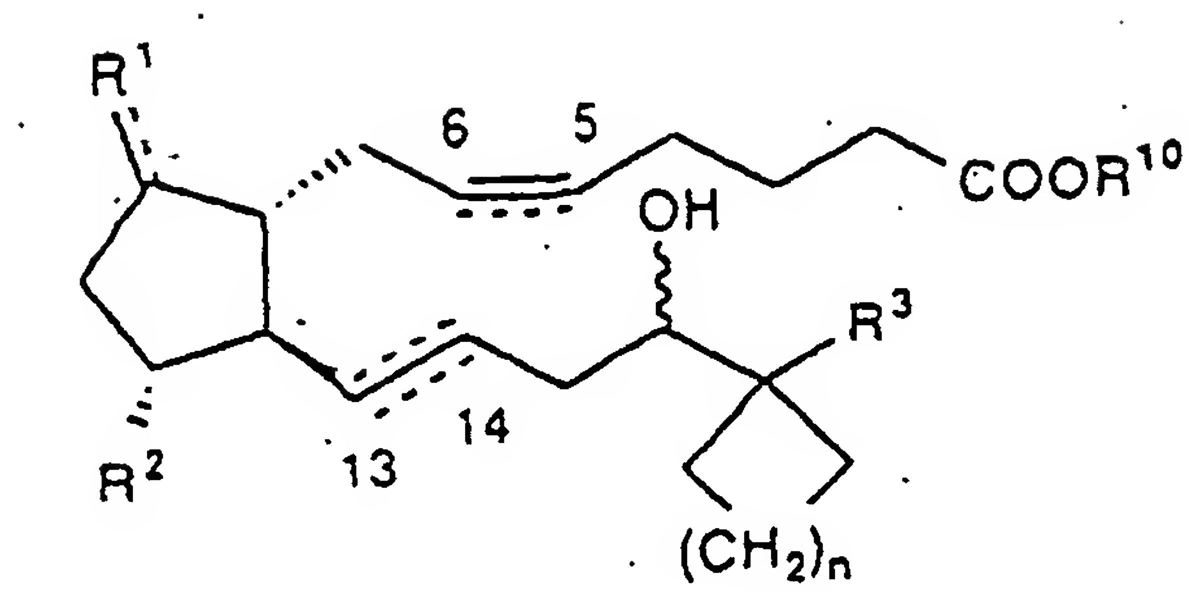


is double bond or triple bond; and

is a single bond, double bond or triple bond;
and wherein the double bond at the 13-14 position, when present, is in the E, Z or EZ mixture form;
with the proviso that when the 5-6 position is a triple bond, the 13-14 position is not a triple bond;
or a non-toxic salt thereof, prodrug thereof or cyclodextrin clathrate thereof, (2) processes for the preparation thereof, and
(3) pharmaceutical agents containing such a derivative as an active ingredient

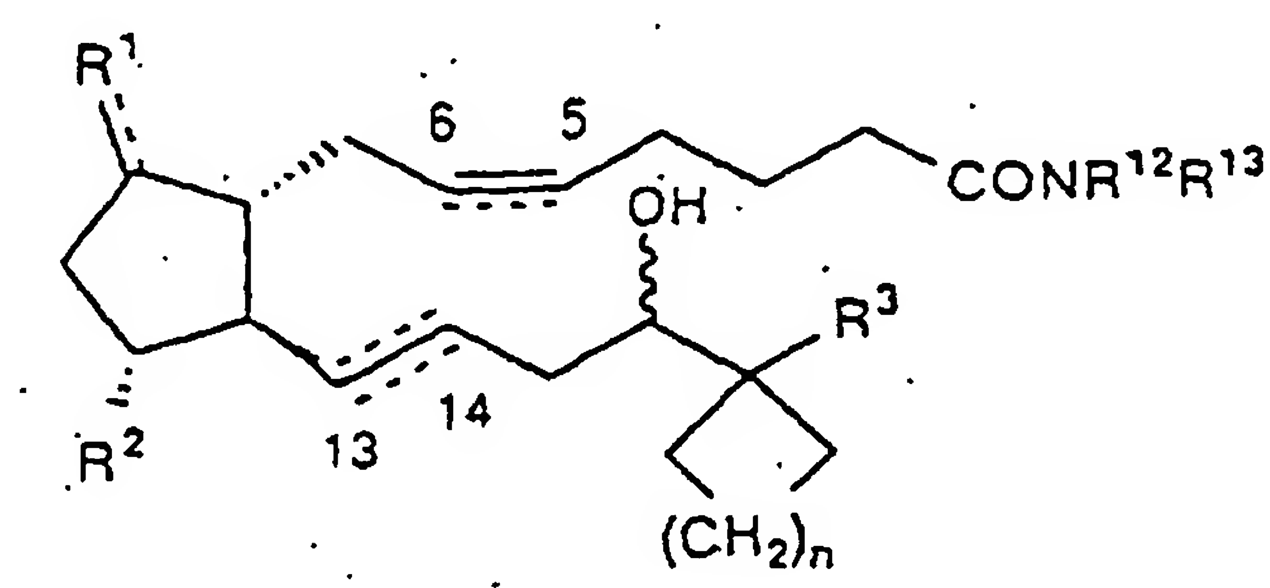
[0010] In the present invention, prodrug means

1) for compounds of formula (I) of the present invention, those in which R represents $COOR^{10}$ (in which R^{10} is C1-6 alkyl), i.e. the compounds of formula (IA)



(IA)

wherein all symbols are as hereinbefore defined, or 2) for compounds of formula (I) of the present invention, those in which R represents $CONR^{12}R^{13}$ (in which R^{12} and R^{13} each, independently, is hydrogen atom or C1-6 alkyl), i. e., the compounds of formula (IB)



(IB)

wherein all symbols are as hereinbefore defined.

[0011] In formula (I), C1-4 alkyl in the definitions of R^3, R^{11} and R^{14} means methyl, ethyl, propyl, butyl and isomers thereof.

[0012] In formula (I), (IA) or (IB), C1-6 alkyl represented by R^{10}, R^{12} and R^{13} means methyl ethyl, propyl, butyl, pentyl, hexyl and isomers thereof.

[0013] In formula (I), C1-8 alkyl represented by R^3 means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomers thereof.

[0014] In formula (I), C2-4 alkenyl in the definition of R^{11} means vinyl, propenyl, butenyl and isomers thereof.

[0015] In formula (I), C2-8 alkenyl represented by R^3 means vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and isomers thereof.

[0016] In formula (I), C2-8 alkynyl represented by R^3 means ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and isomers thereof.

[0017] In formula (I), C1-4 alkoxy in the definitions of R^2, R^{11} and R^3 means methoxy, ethoxy, propoxy, butoxy and isomers thereof.

[0018] In formula (I), C3-7 cycloalkyl in the definition of R^3 means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0019] In formula (I), a halogen atom in the definition of R^1 and R^3 means fluorine, chlorine, bromine and iodine

[0020] In the present invention, it may be easily understood by these skilled in the art, unless otherwise specified, the symbol

indicates that the substituent attached thereto is in front of the sheet, unless otherwise specified, the symbol:

indicates that the substituent attached thereto is behind the sheet, unless otherwise specified, the symbol:

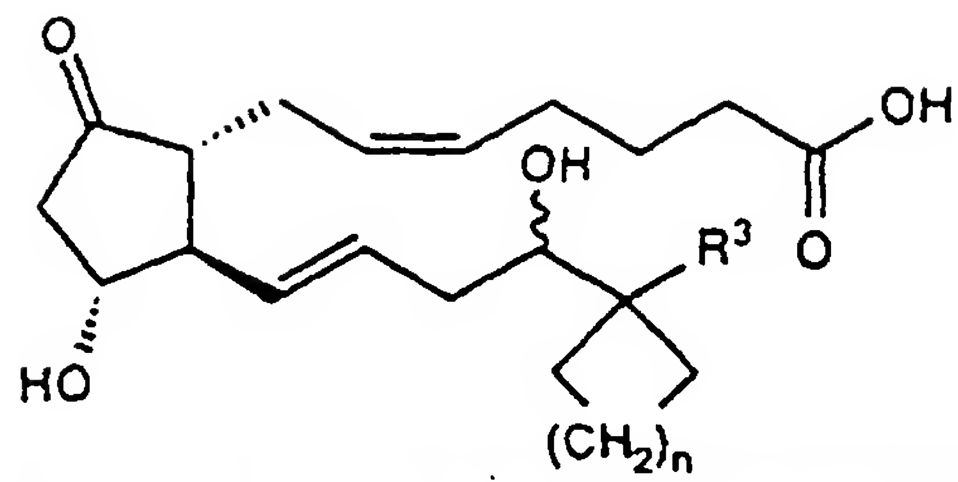
 or 

indicates that the substituent attached thereto is a mixture of in front of and behind the sheet or may be in front of or behind the sheet.

[0021] Unless otherwise specified, all isomers are included in the present invention. For example, the alkyl, alkenyl and alkynyl groups include straight-chain and also branched-chain ones The double bond in alkenyl group includes E, Z and EZ mixtures. Isomers generated by the existence of asymmetric carbon atom(s) e.g. in branched-chain alkyl are included in the present invention.

[0022] Preferred compounds of the present invention include compounds of the formula (I) listed in the examples or in Tables 1-14 or prodrugs thereof.

[Table 1]



(Ia)

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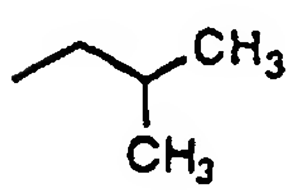
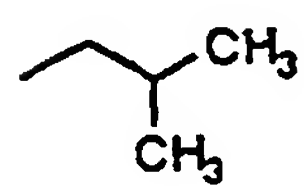
2	0		12	1	
3	0		13	1	
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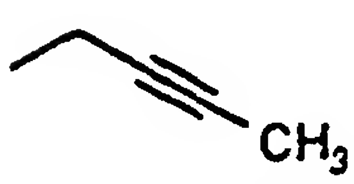
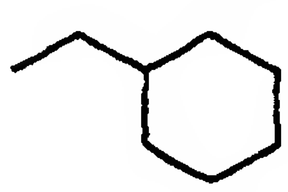
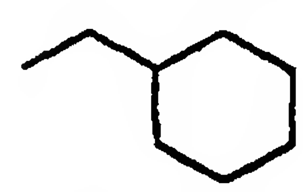
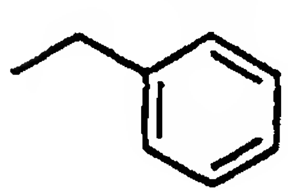
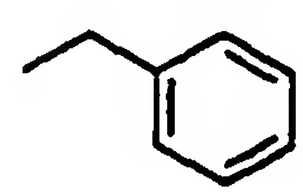
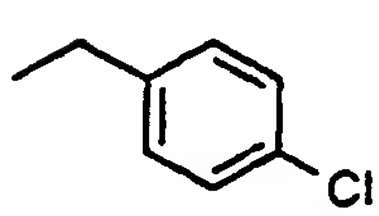
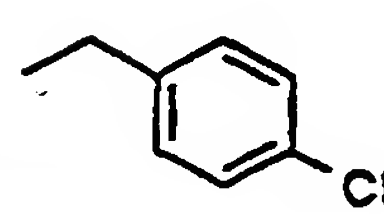
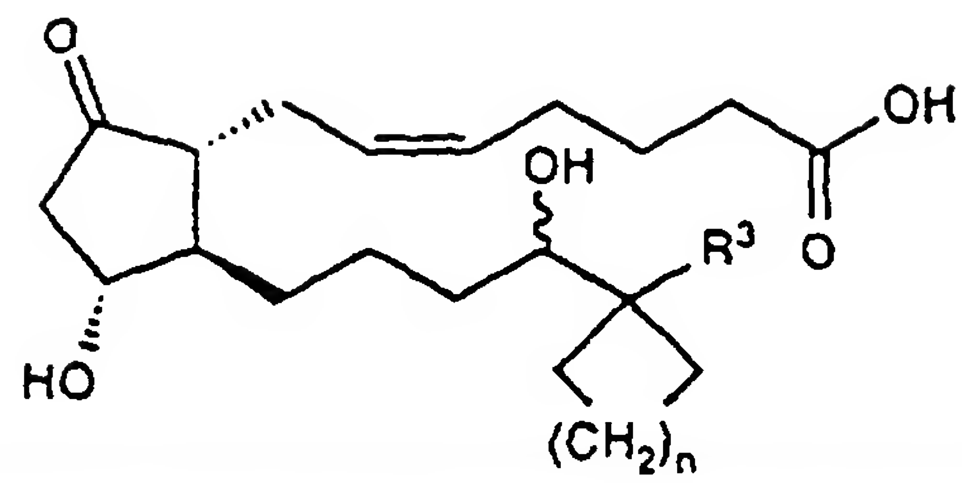
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

[Table 2]



(Ib)

No.	n	R^3	No.	n	R^3
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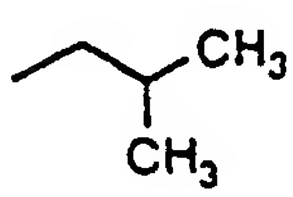
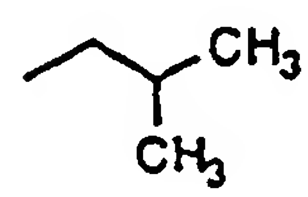
3	0		13	1	
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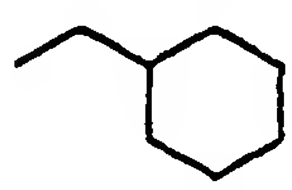
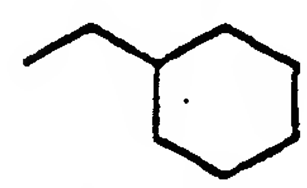
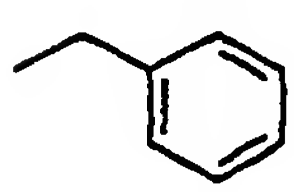
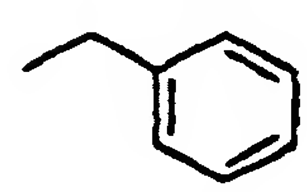
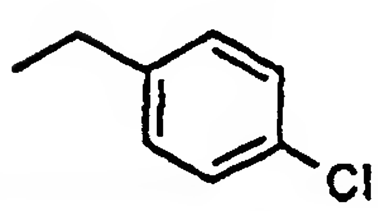
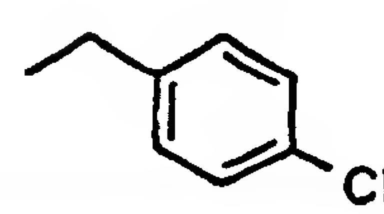
8	0		18	1	
9	0		19	1	
10	0		20	1	

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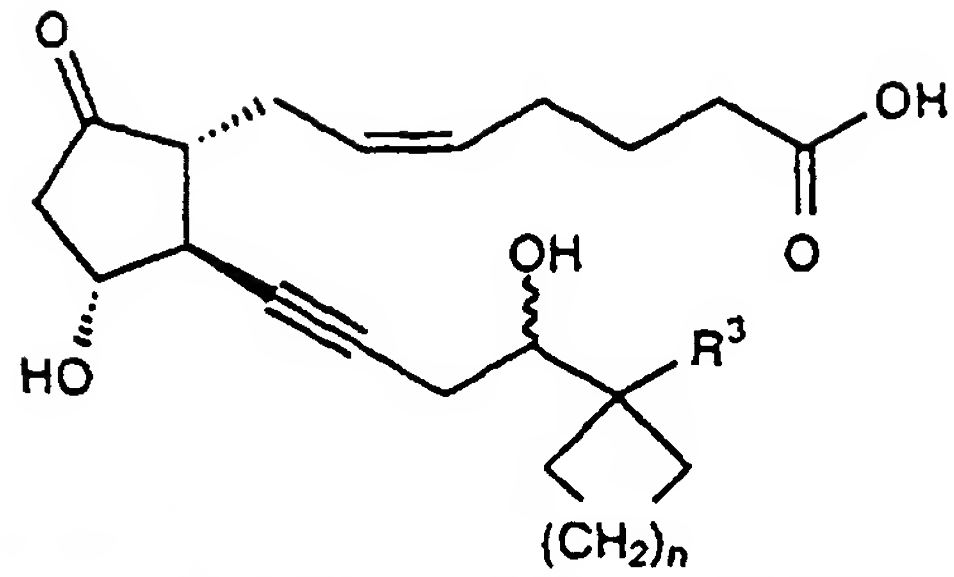

(Ic)

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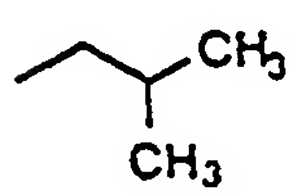
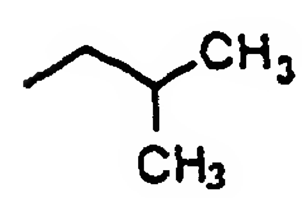
3	0		13	1	
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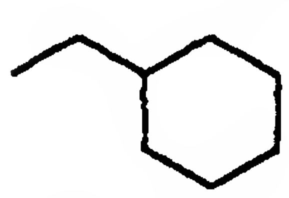
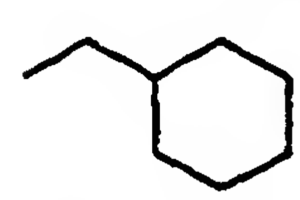
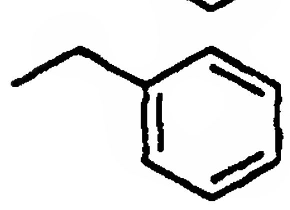
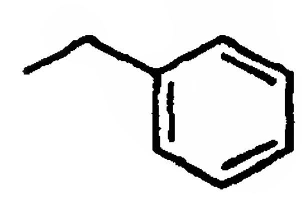
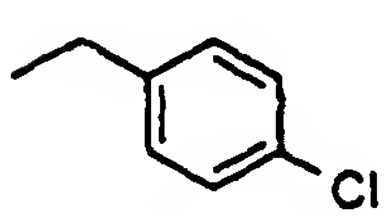
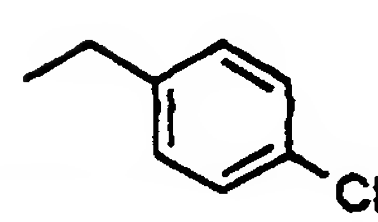
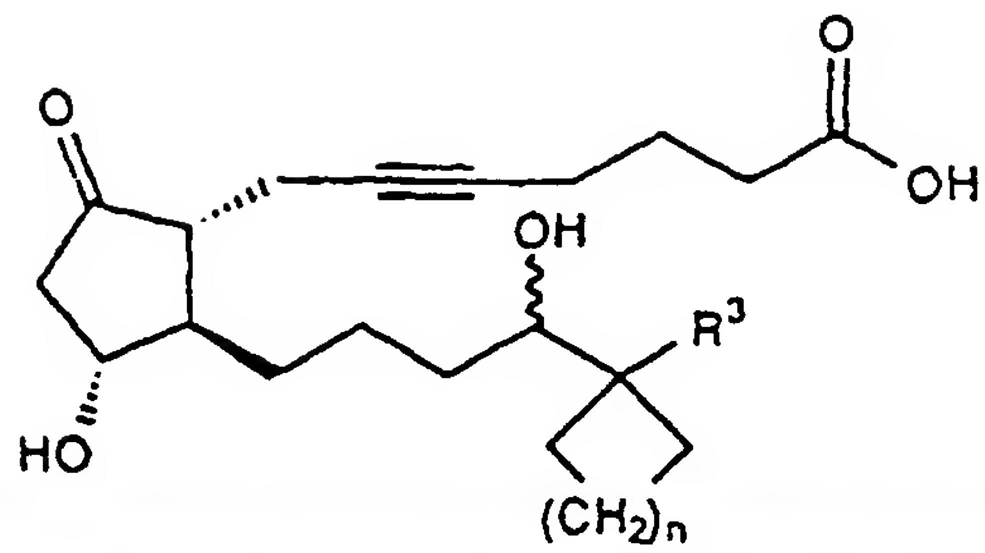
8	0		18	1	
9	0		19	1	
10	0		20	1	

[Table 4]



(Id)

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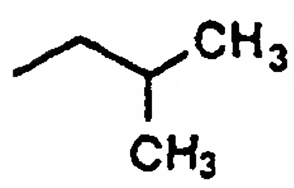
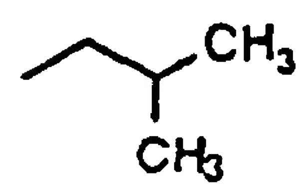
3	0		13	1	
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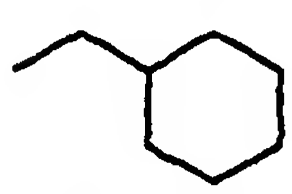
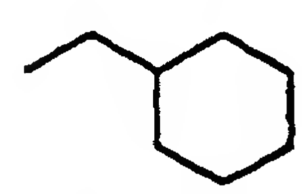
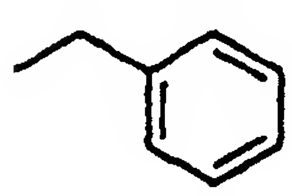
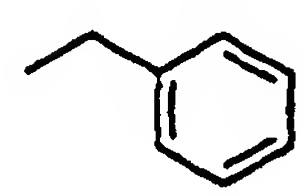
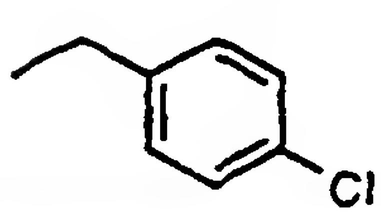
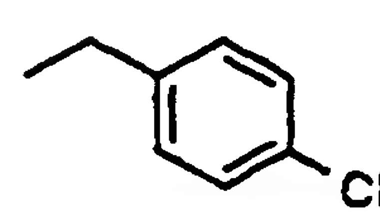
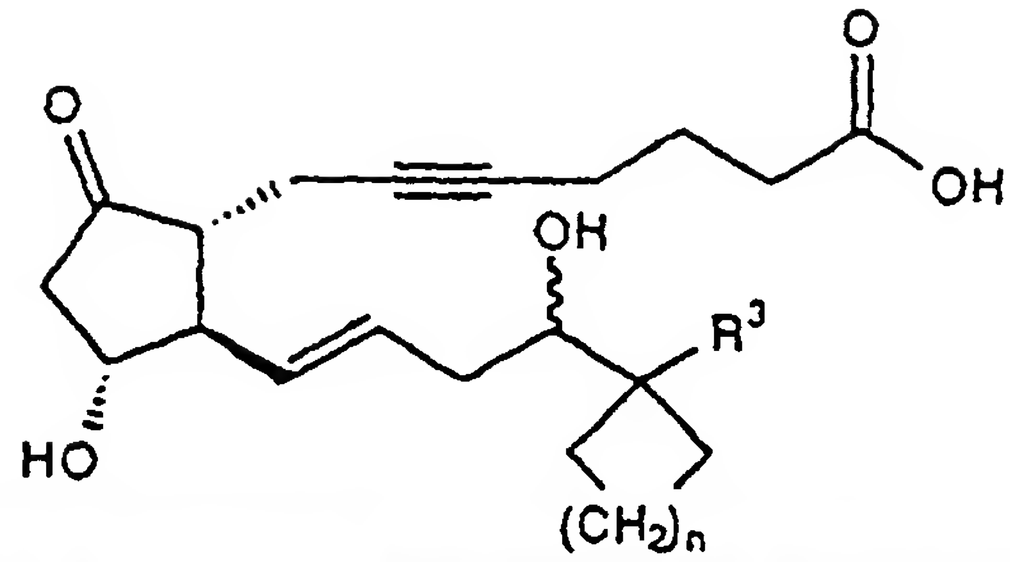
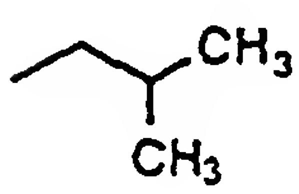
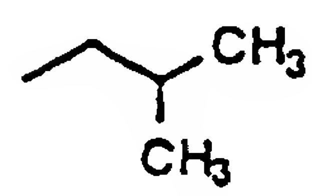
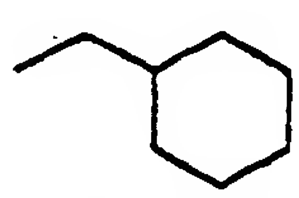
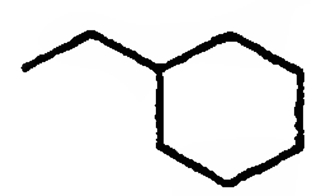
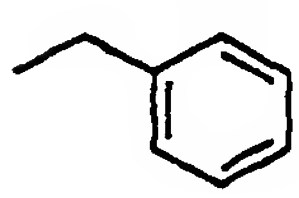
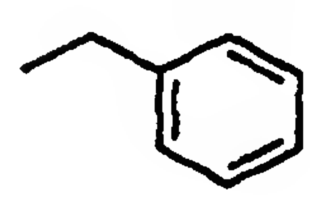
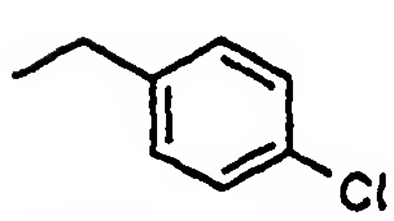
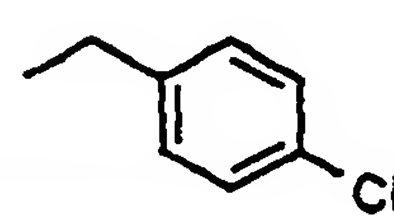
8	0		18	1	
9	0		19	1	
10	0		20	1	

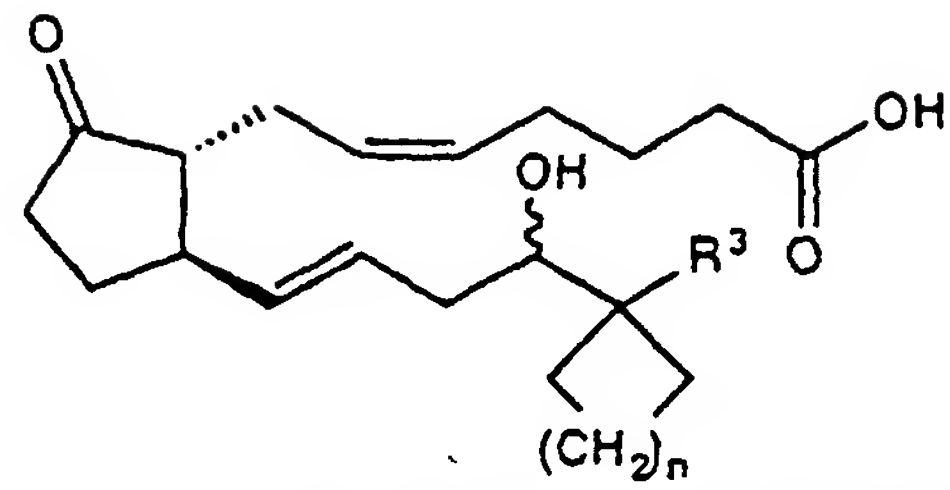
[Table 5]



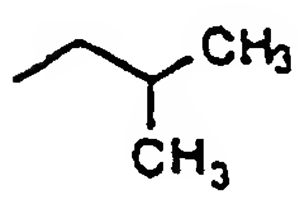
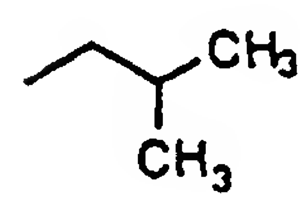
(Ie)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

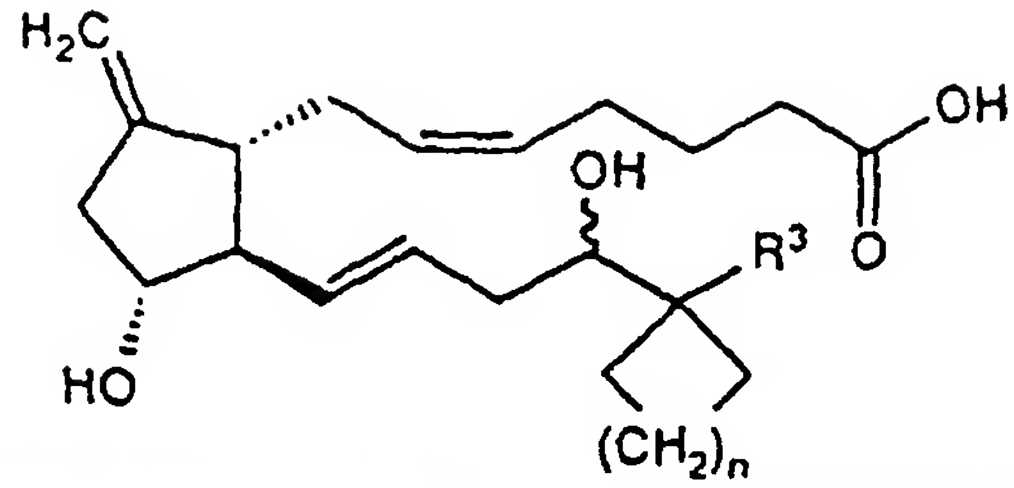
[Table 6]



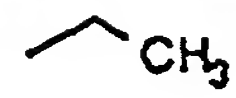
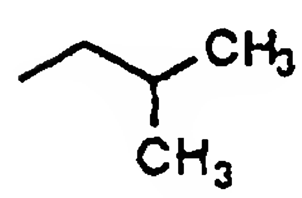
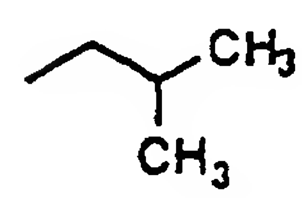
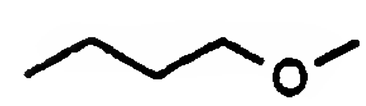
(II)

No.	n	R³	No.	n	R³
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

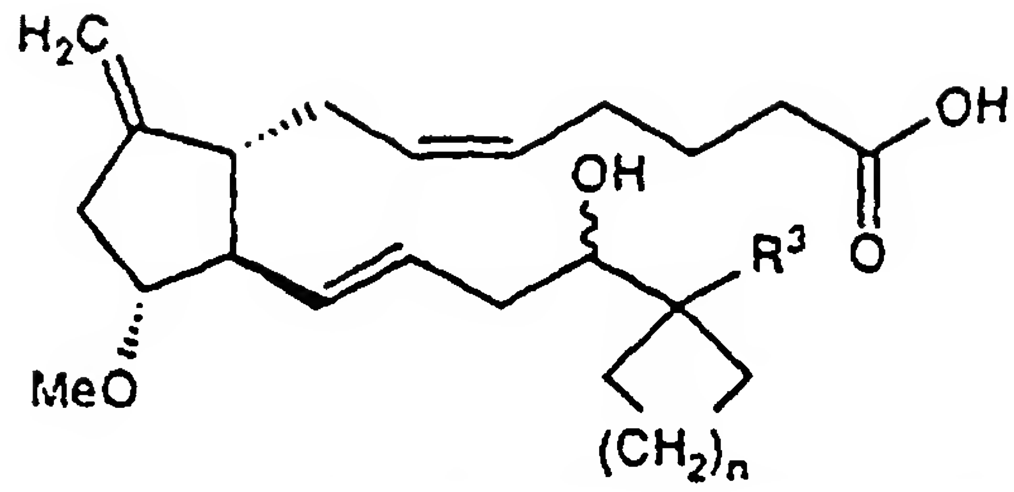
[Table 7]



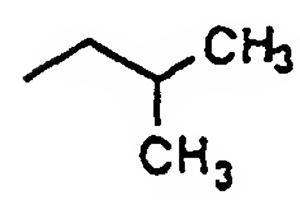
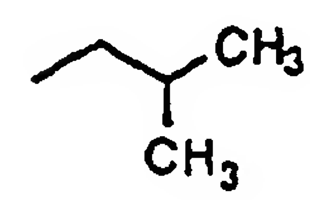
(Ig)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

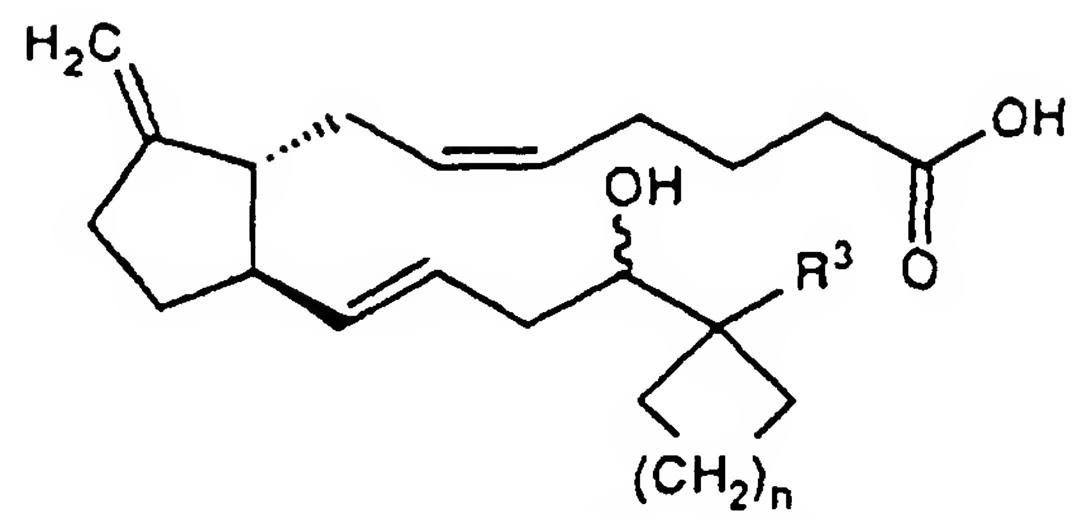
[Table 8]



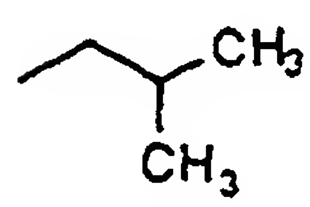
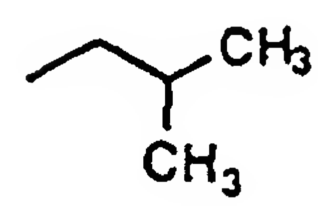
(Ih)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

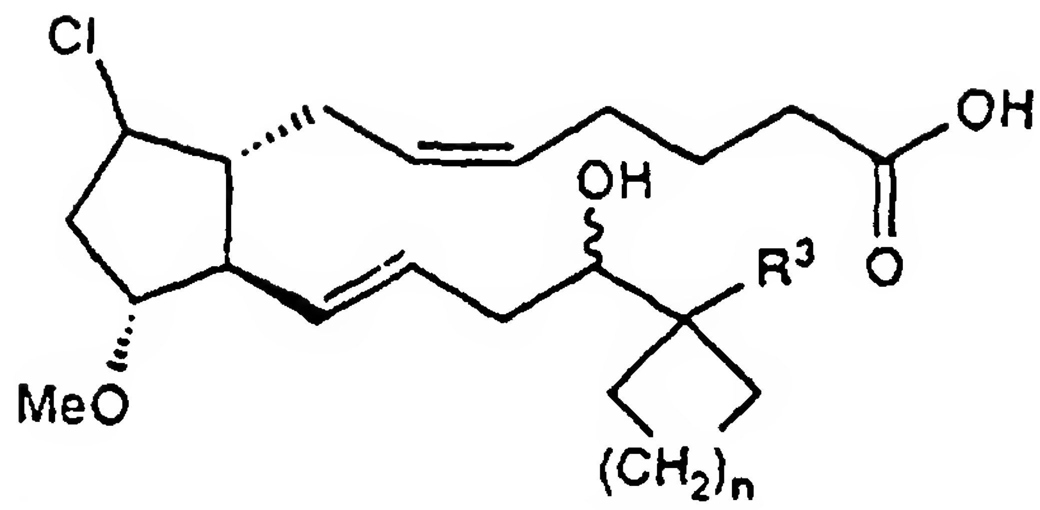
[Table 9]



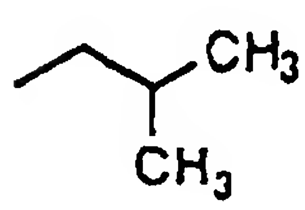
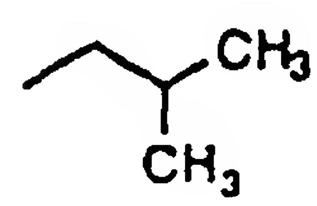
(Ii)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

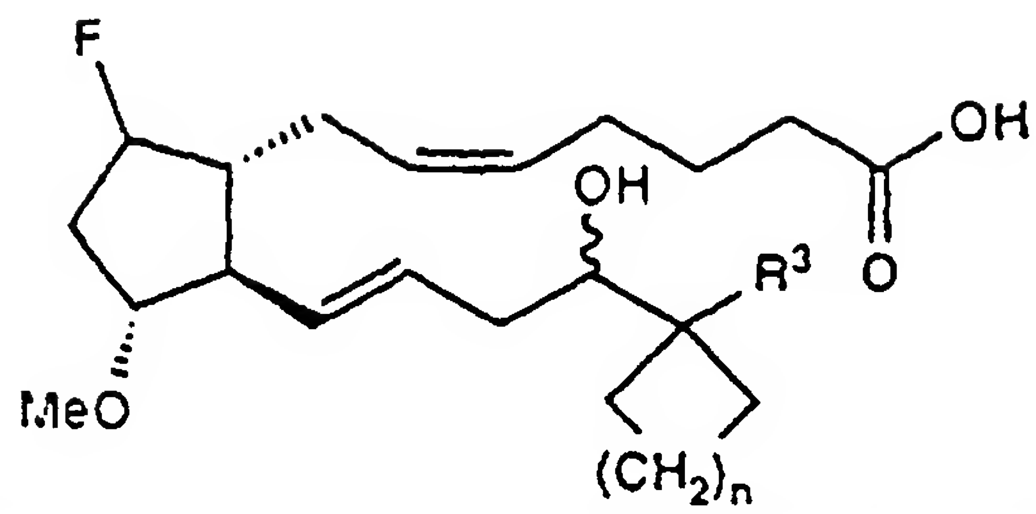
[Table 10]



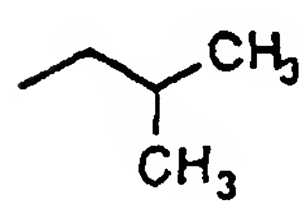
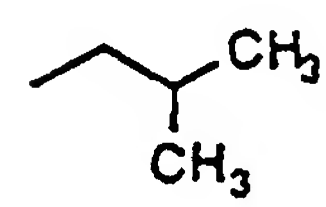
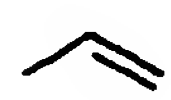
(Ij)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

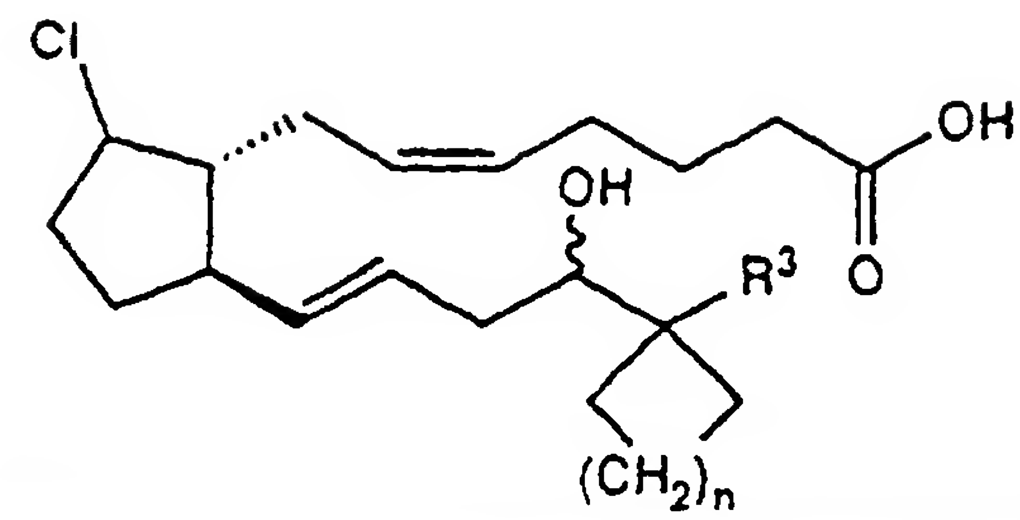
[Table 11]



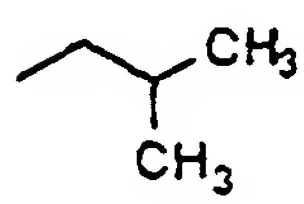
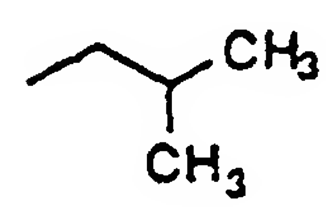
(Ik)

No.	n	R3	No.	n	R3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

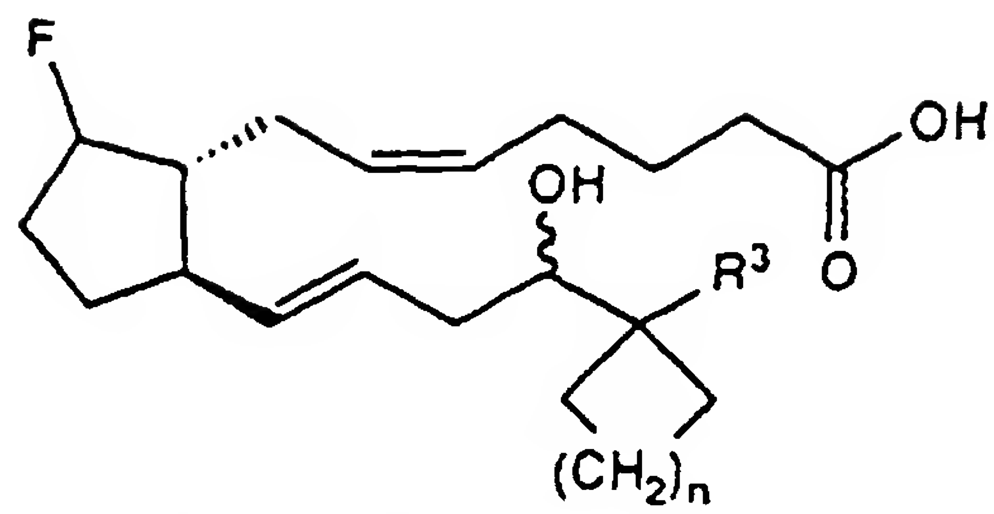
[Table 12]



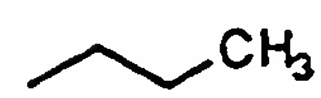
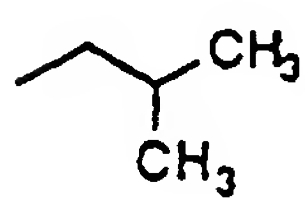
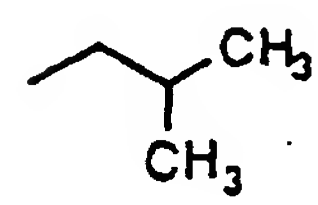
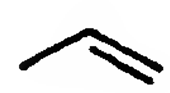
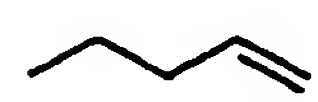
(II)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

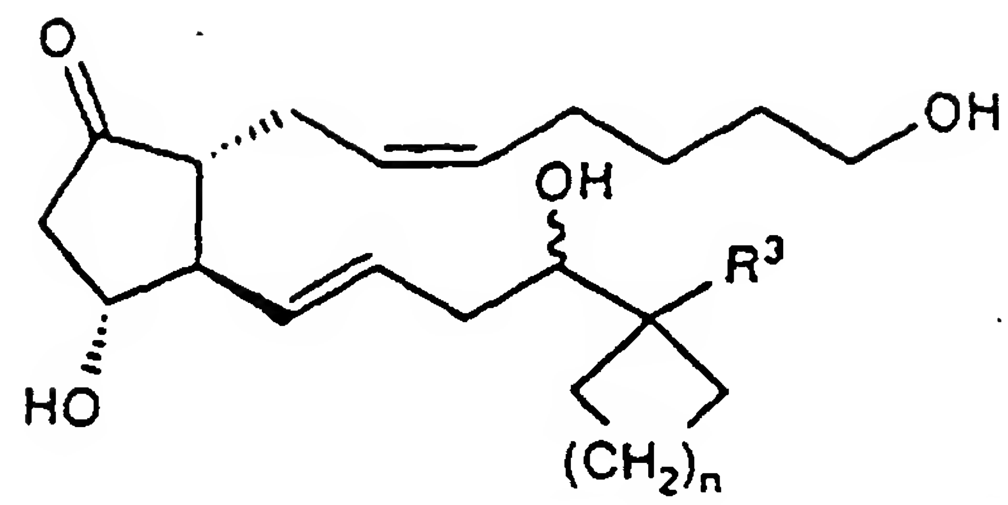
[Table 13]



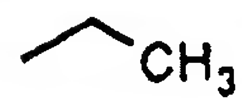
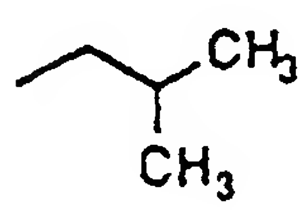
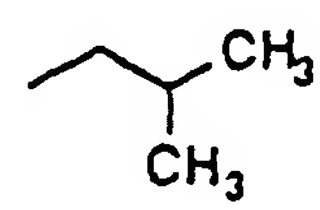
(Im)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

[Table 14]



(In)

No.	n	R^3	No.	n	R^3
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

Salts

[0023] The compounds of formula (I) of the present invention may be converted into a corresponding non-toxic salt by methods known per se. Non toxic and water-soluble salts are preferable. Suitable salts, for example, are salts of an alkali metal (potassium, sodium etc.), salts of an alkaline earth metal (calcium, magnesium etc.), ammonium salts and salts of pharmaceutically-acceptable organic amines (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine etc.).

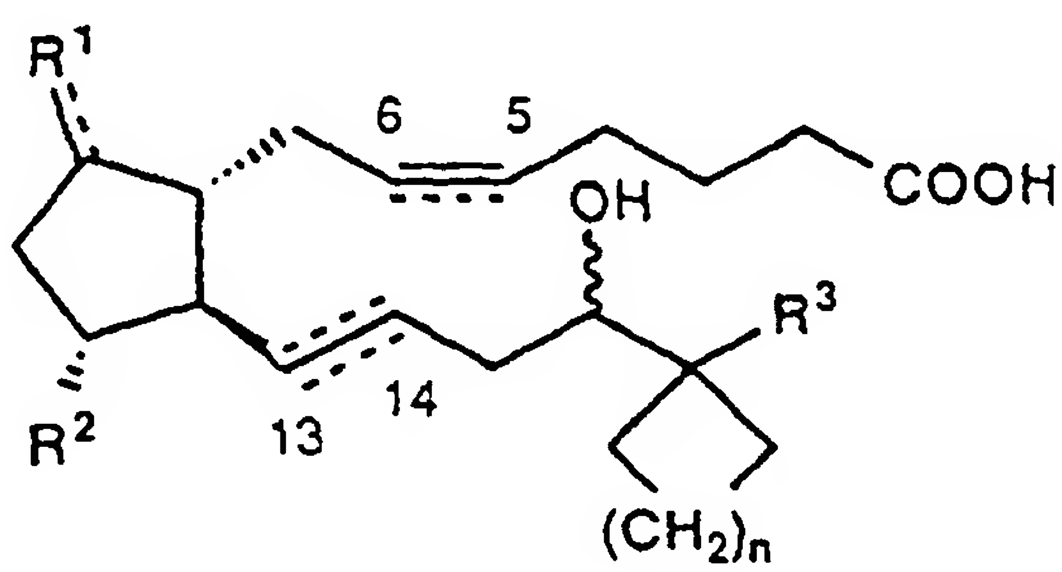
Cyclodextrin clathrates

[0024] Cyclodextrin clathrates of ω-cycloalkyl-prostaglandin E_2 derivatives of the formula (I) may be prepared by the method described in the specification of GB 1 351 238, which is herein incorporated by reference, using α-, β- or γ-cyclodextrin or a mixture thereof. Converting into their cyclodextrin clathrates serves to increase the stability and solubility in water of the compounds, and is therefore useful in the use for pharmaceuticals.

Processes for the Preparation

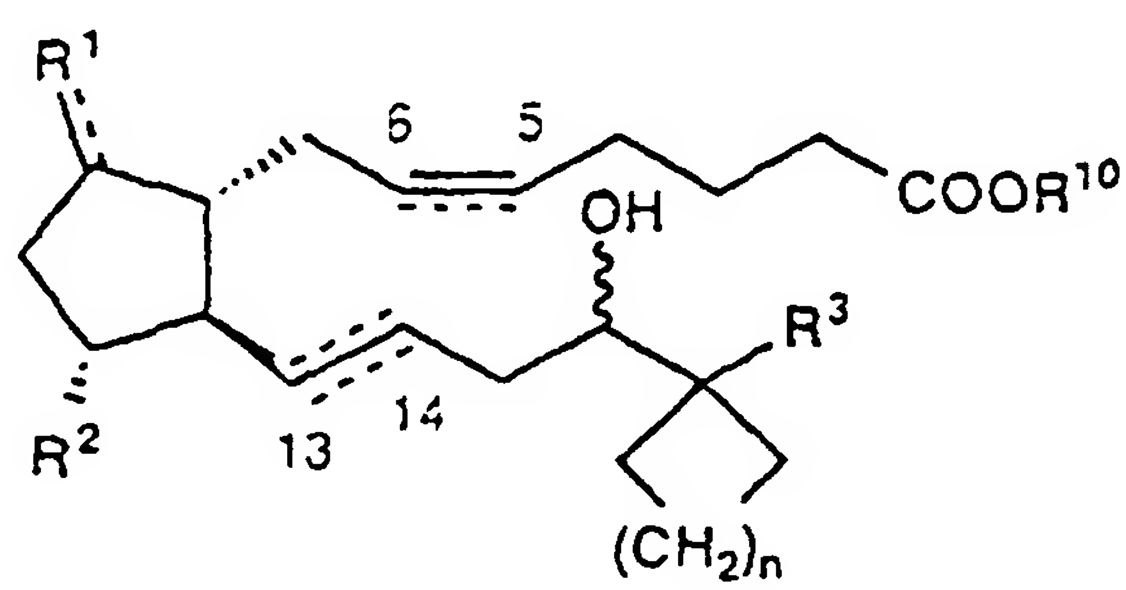
1) For compounds of formula (I) of the present invention, those in which R is carboxy, i.e., the compounds of formula (I-1)

[0025]



(I-1)

wherein all the symbols are as hereinbefore defined may be prepared by hydrolysis using an enzyme or hydrolysis under alkaline conditions of a compound of formula (IA)



(IA)

wherein all the symbols are as hereinbefore defined.

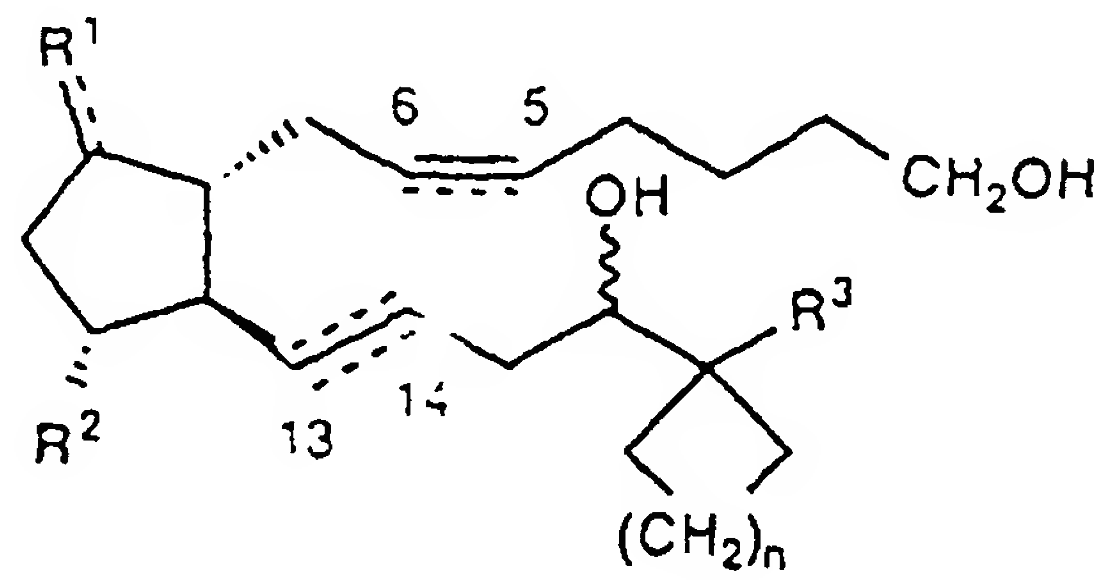
[0026] The hydrolysis using an enzyme is known. For example, hydrolysis may be carried out in a mixture of a water-miscible organic solvent (ethanol, dimethylsulfoxide etc.) and water, in the presence or absence of buffer, using an ester cleaving enzyme (esterase, lipase etc.), at a temperature of from 0 °C to 50 °C.

[0027] The hydrolysis under alkaline conditions is known. For example, hydrolysis may be carried out in a water-miscible organic solvent (ethanol, tetrahydrofuran, dioxan etc.); using aqueous solution of an alkali (sodium hydroxide,

potassium hydroxide, potassium carbonate etc.), at a temperature of from -10 to 90 °C.

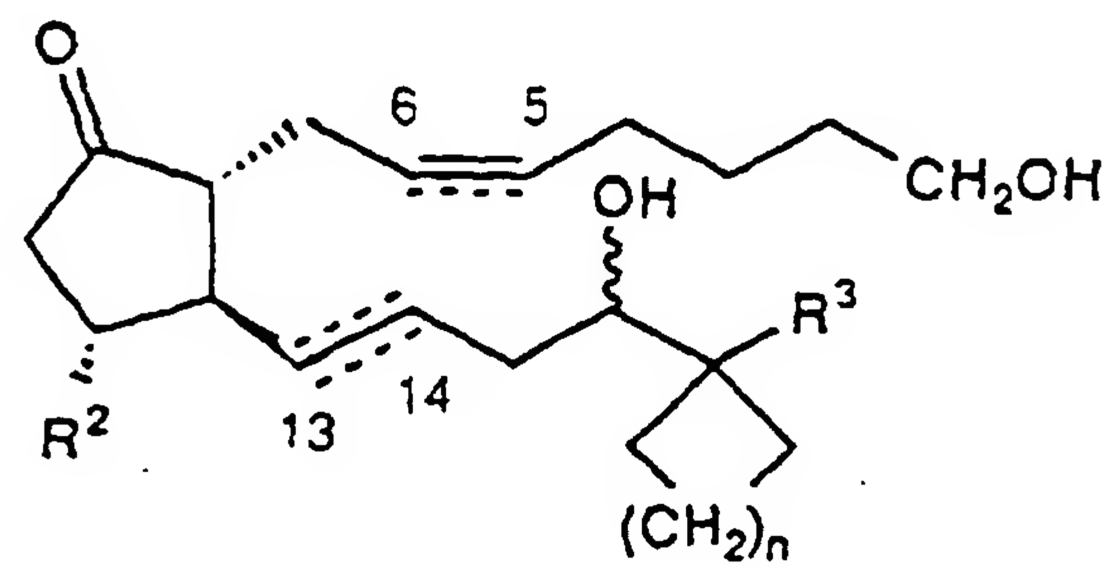
2) For compounds of formula (I) of the present invention, those in which R is hydroxymethyl and R^1 is oxo, i.e. in the compounds of formula (I-2),

[0028]



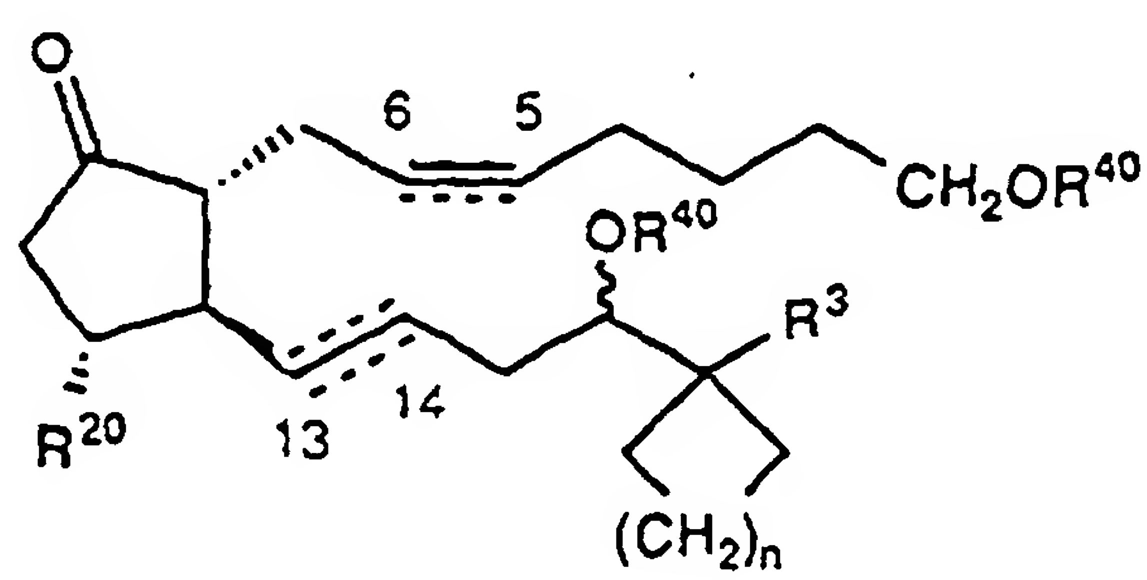
(I-2)

wherein all the symbols are as hereinbefore defined
those in which R^1 is oxo, i.e., the compounds of formula (I-2A)



(I-2A)

wherein all the symbols are as hereinbefore defined may be prepared by elimination under acidic conditions of the protecting group(s) of a compound of formula (IIA)



(IIA)

wherein R^{20} is hydrogen atom, hydroxy protecting group which may be eliminated under acidic conditions or C1-4 alkoxy, R^{40} is hydroxy protecting group which may be eliminated under acidic conditions, and the other symbols are as hereinbefore defined.

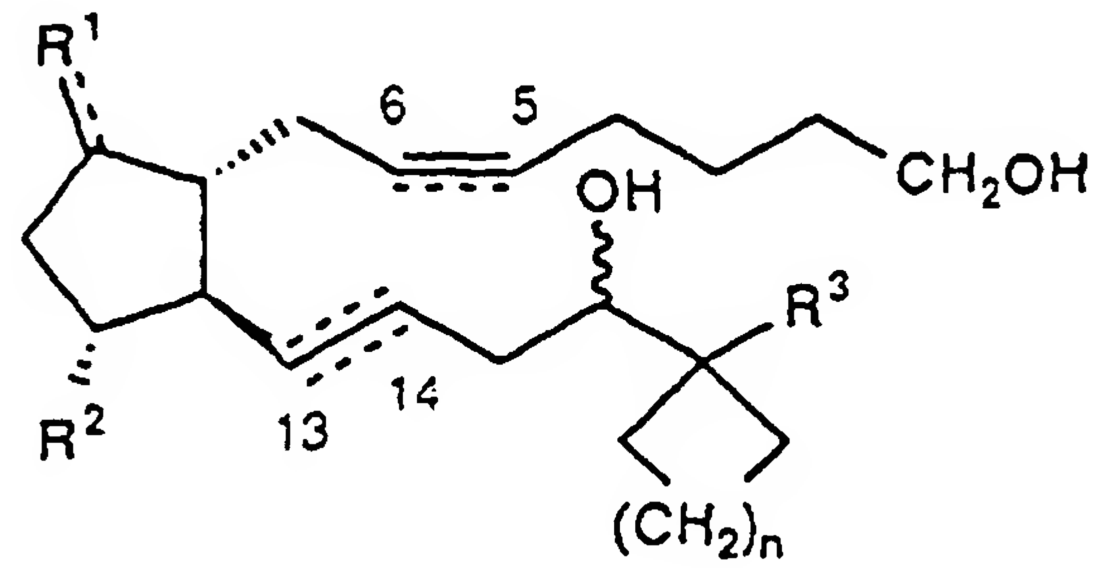
[0029] The hydroxy protecting group which may be eliminated under acidic conditions includes, for example, t-butyld-

imethylsilyl, triphenylmethyl, tetrahydropyran-2-yl etc.

[0030] The hydrolysis under acidic conditions is known. For example, hydrolysis may be carried out in a water-miscible organic solvent (tetrahydrofuran, methanol, ethanol, dimethoxyethane, acetonitrile or mixture thereof etc.), using an inorganic acid (hydrochloric acid, phosphoric acid, hydrofluoric acid or hydrogen fluoride-pyridine etc.), or organic acid (acetic acid, p-toluenesulfonic acid, trichloroacetic acid, etc.) at a temperature of from 0 to 50 °C.

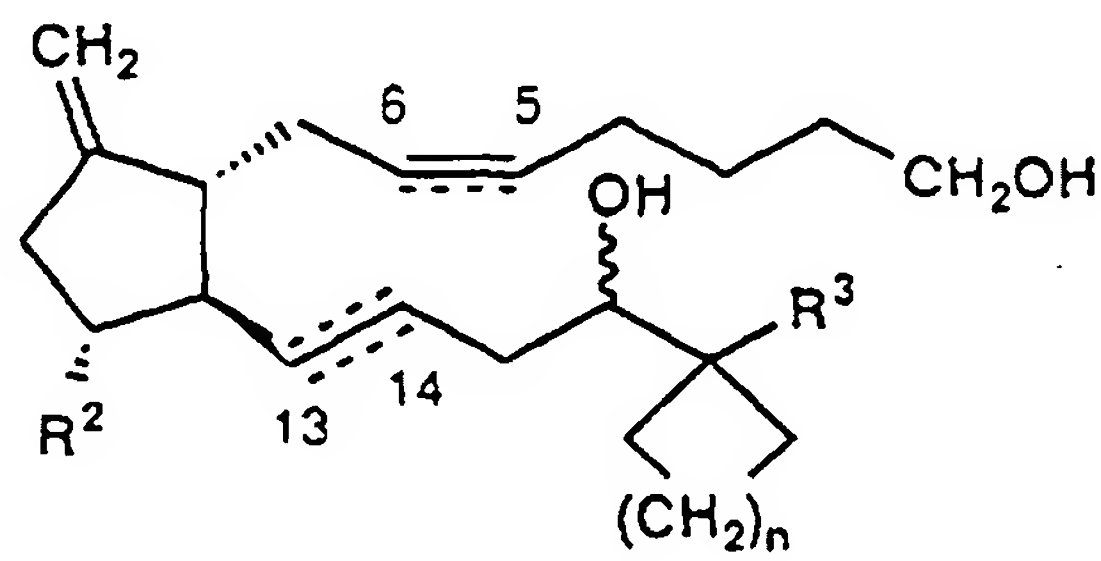
3) For compounds of formula (I) of the present invention, those in which R is hydroxymethyl and R^1 is methylene, i.e., in the compounds of formula (I-2)

[0031]



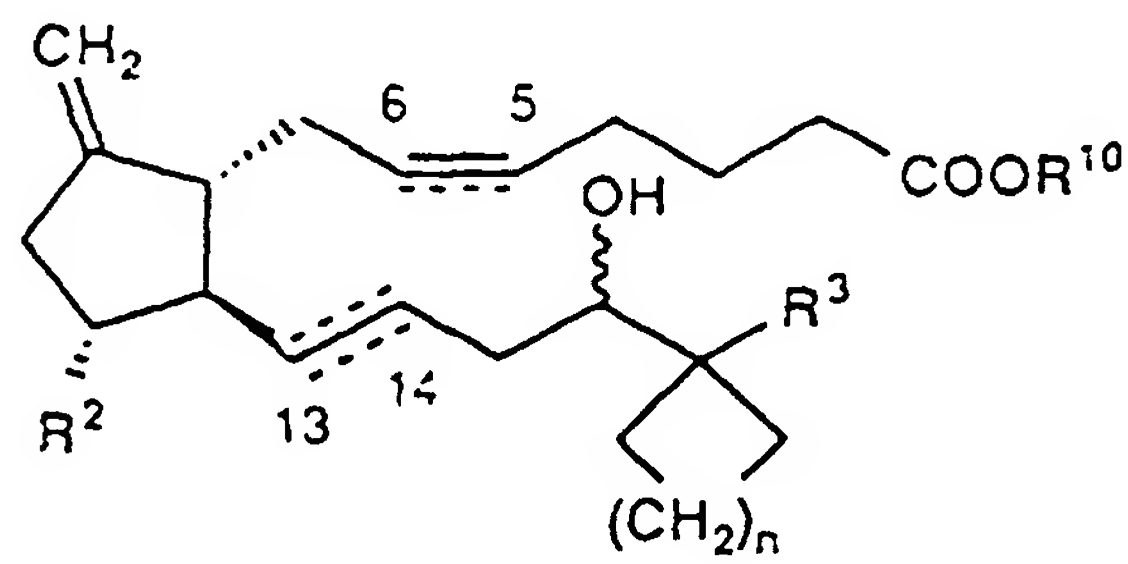
(I-2)

wherein all the symbols are as hereinbefore defined
these in which R^1 is methylene, i.e., the compounds of formula (I-2B)



(I-2B)

wherein all the symbols are as hereinbefore defined may be prepared by reduction of a compound of formula (IA-4)



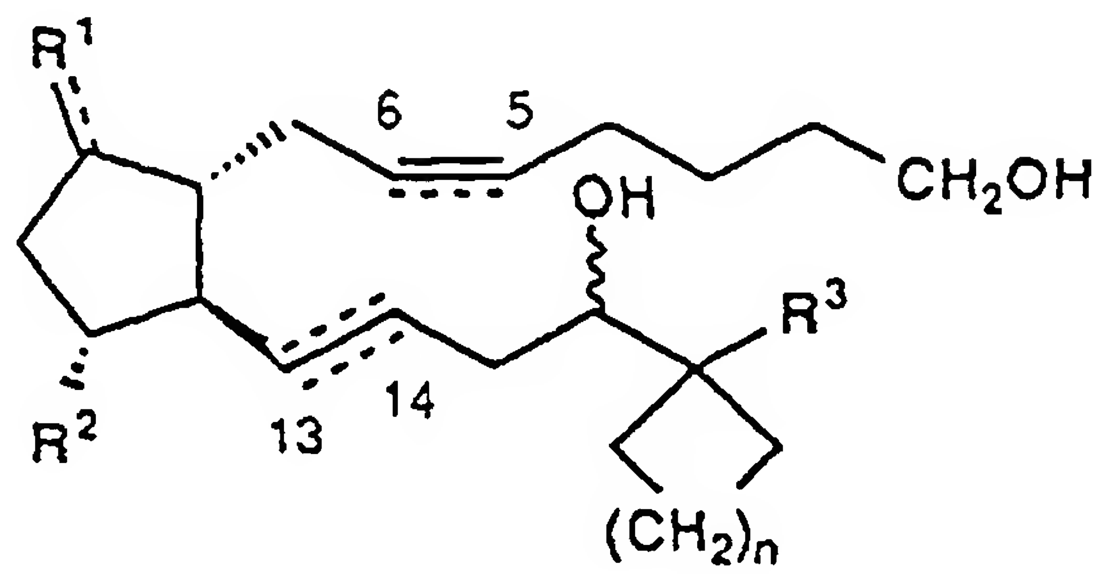
(IA-4)

wherein all the symbols are as hereinbefore defined.

[0032] The reduction is known. For example, reduction may be carried out in an inert organic solvent (tetrahydrofuran (THF), hexane, toluene, etc.), using diisobutylaluminum hydride at a temperature of from -80 to 0 °C.

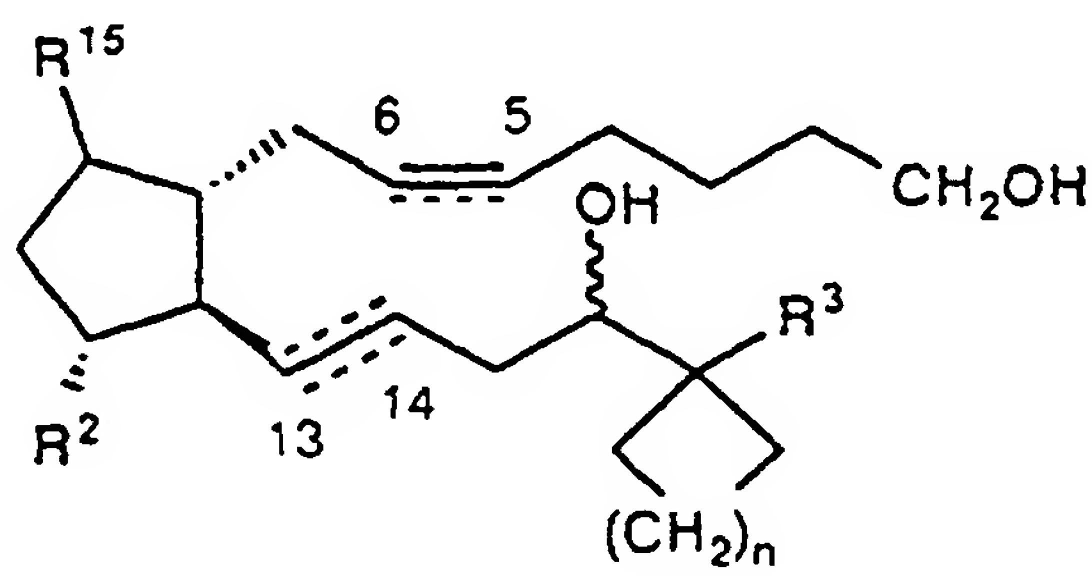
4) For compounds of formula (I) of the present invention, those in which R is hydroxymethyl and R^1 is halogen atom, i.e., in the compounds of formula (1-2)

[0033]



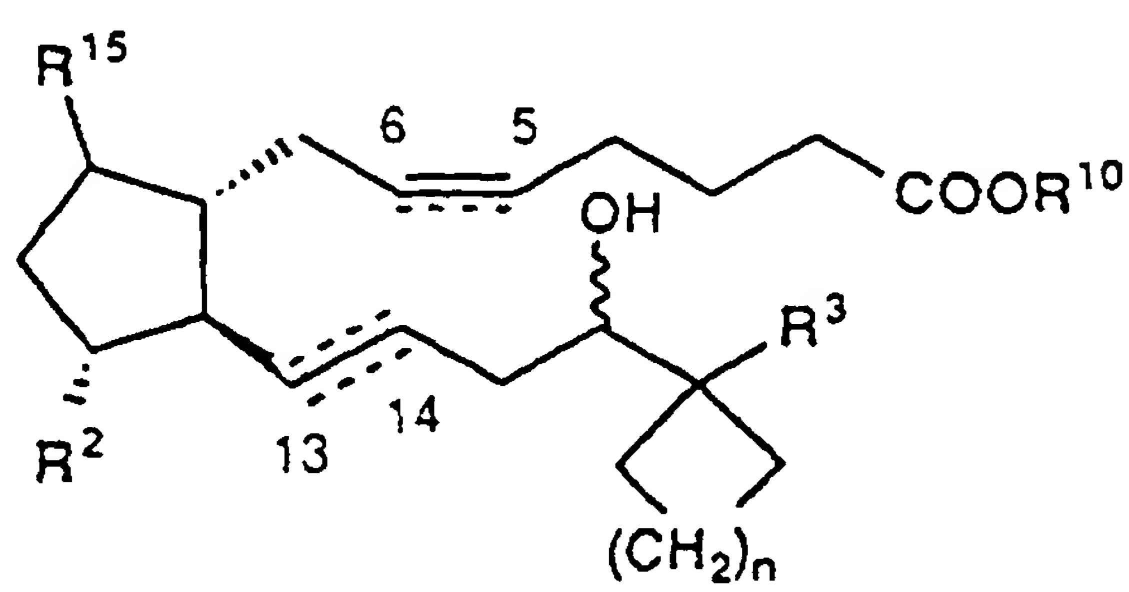
(I-2)

wherein all the symbols are as hereinbefore defined
those in which R^1 is halogen atom, i.e., the compounds of formula (I-2C)



(I-2C)

wherein R^{15} is halogen atom and the other symbols are as hereinbefore defined
may be prepared by reduction of a compound of formula (IA-5)

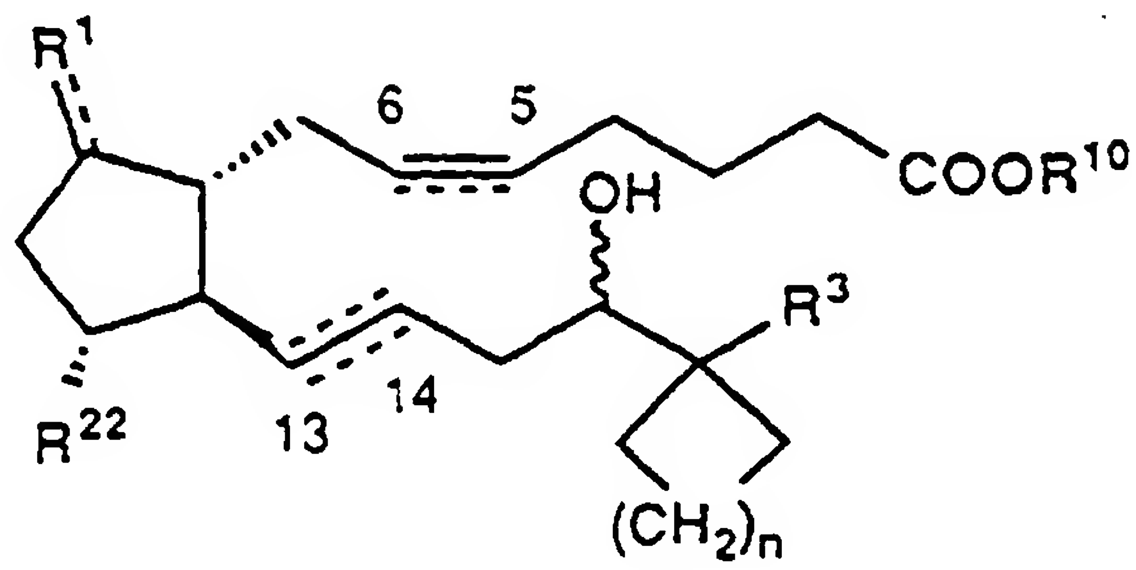


(IA-5)

wherein all the symbols are as hereinbefore defined.
[0034] The reduction may be carried out by the same method as hereinbefore described.

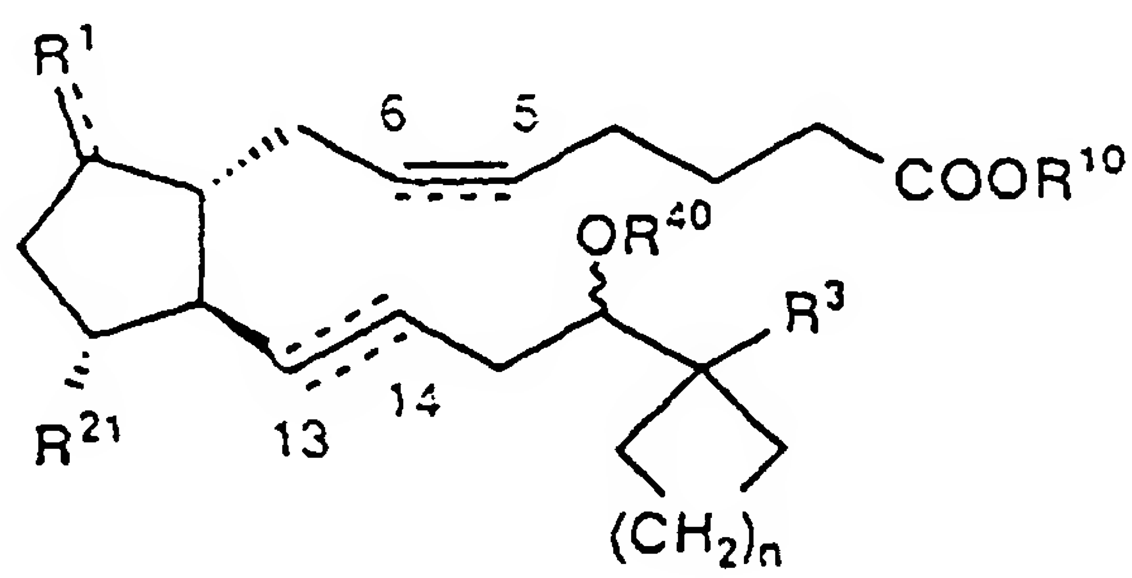
5) For prodrug compounds of formula (IA) of the present invention, those in which R^2 is hydrogen atom or hydroxy, i. e., the compounds of formula (IA-1)

[0035]



(IA-1)

wherein R^{22} is hydrogen atom or hydroxy and the other symbols are as hereinbefore defined may be prepared by hydrolysis under acidic conditions of a compound of formula (III)



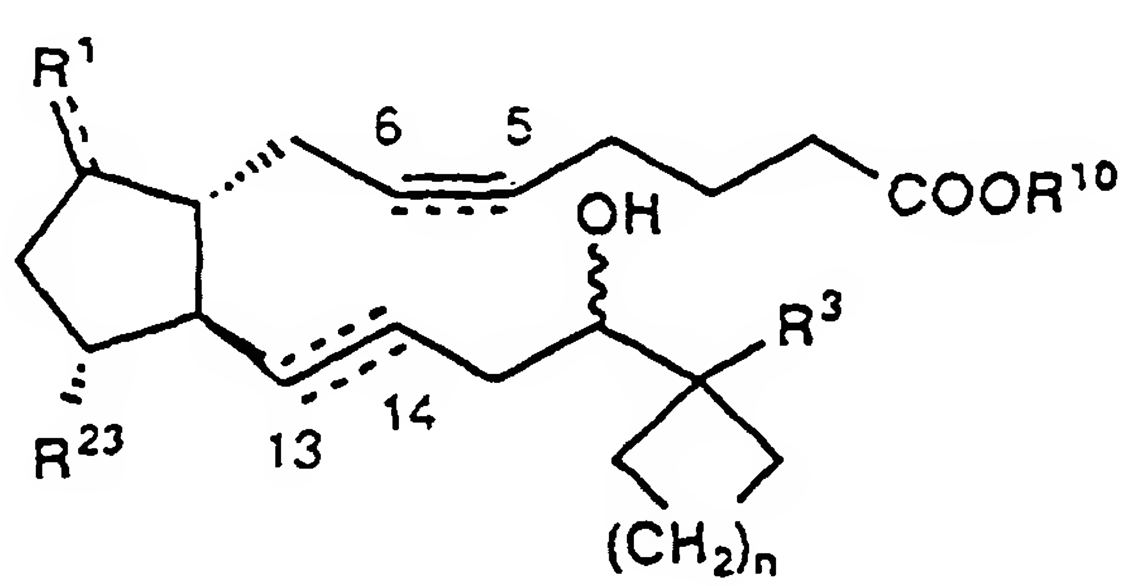
(III)

wherein R^{21} is hydrogen atom or hydroxy protecting group which may be eliminated under acidic conditions, and the other symbols are as hereinbefore defined.

[0036] The hydrolysis under acidic conditions may be carried out by the same method as hereinbefore described.

6) For prodrug compounds of formula (IA) of the present invention, those in which R^2 is C1-4 alkoxy, i.e., the compounds of formula (IA-2)

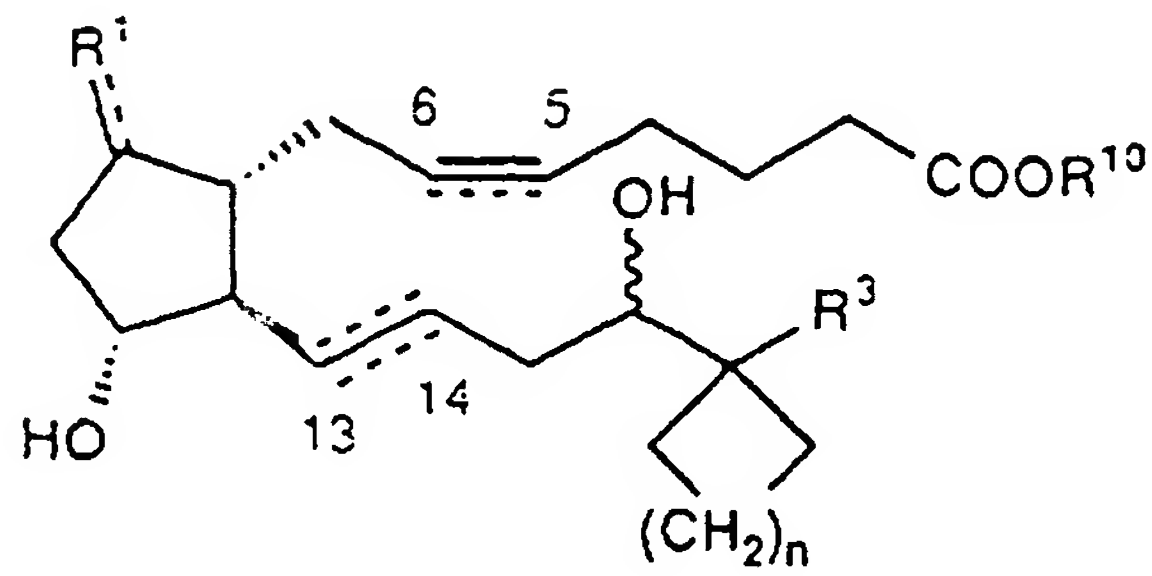
[0037]



(IA-2)

wherein R^{23} is C1-4 alkoxy and the other symbols are as hereinbefore defined may be prepared by O-alkylation of a

compound of formula (IA-1) in which R^{22} is hydroxy, i.e., a compound of formula (IA-3)



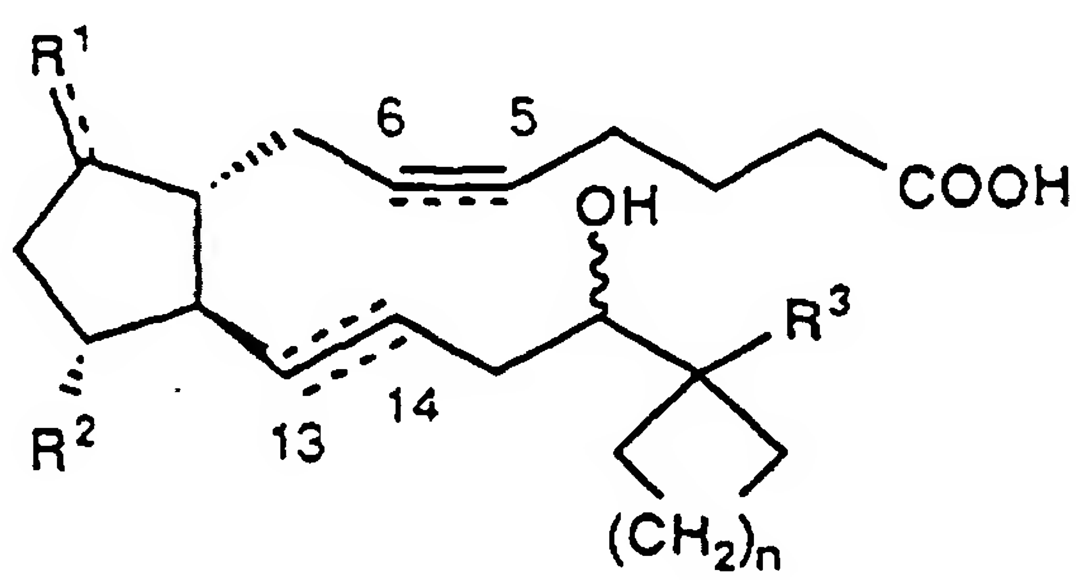
(IA-3)

wherein all the symbols are as hereinbefore defined.

[0038] O-alkylation is known. For example, O-alkylation may be carried out in an inert organic solvent (THF, diethyl ether, etc.), using diazoalkane at a temperature of from -30 to 40 °C or in an inert organic solvent (acetonitrile, etc.), in the presence of silver oxide, using alkyl iodide at a temperature of from 0 to 40 °C.

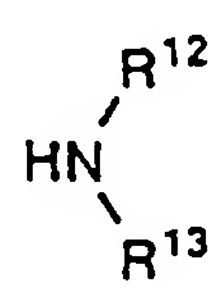
7) The prodrug compounds of formula (IB) of the present invention may be prepared by amidation of a compound of formula (I-1)

[0039]



(I-1)

wherein all the symbols are as hereinbefore defined with a compound of formula (IV)



(IV)

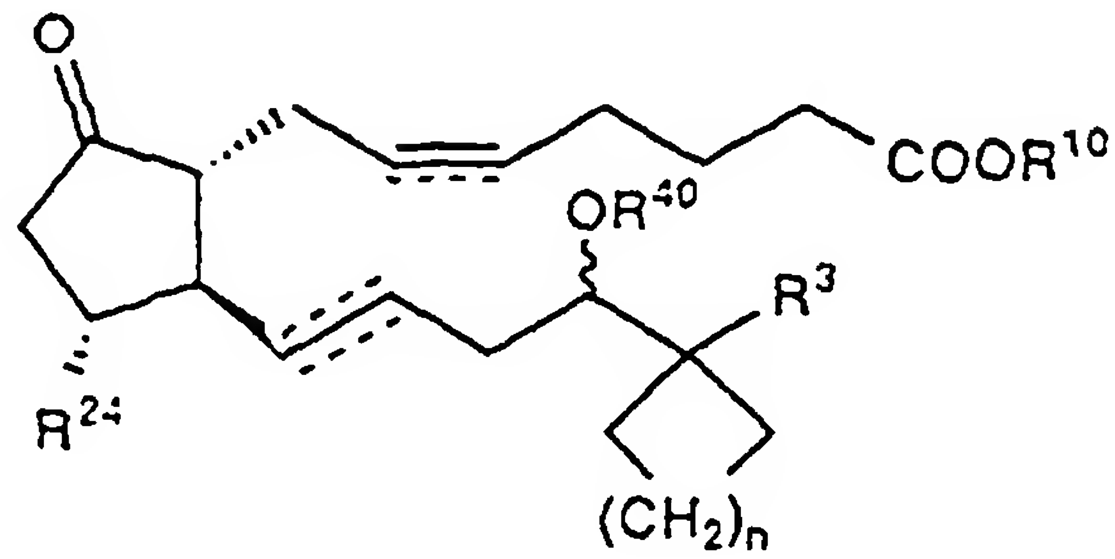
wherein all the symbols are as hereinbefore defined.

[0040] Amidation is known. For example, amidation may be carried out in an inert organic solvent (THF, dichloromethane, benzene, acetone, acetonitrile or mixture thereof etc.), in the presence or absence of tertiary amine(dimethylaminopyridine, pyridine, triethylamine, etc.), using condensing agent (1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimide (EDC), etc.) at a temperature of from 0 to 50 °C.

[0041] The compound of the formula (IIA) may be prepared according to the reaction of the following Scheme (J).

[0042] The compounds of formula (III) may be separated according to the values of R^1 and R^{21} into the following six classes of compounds. That is,

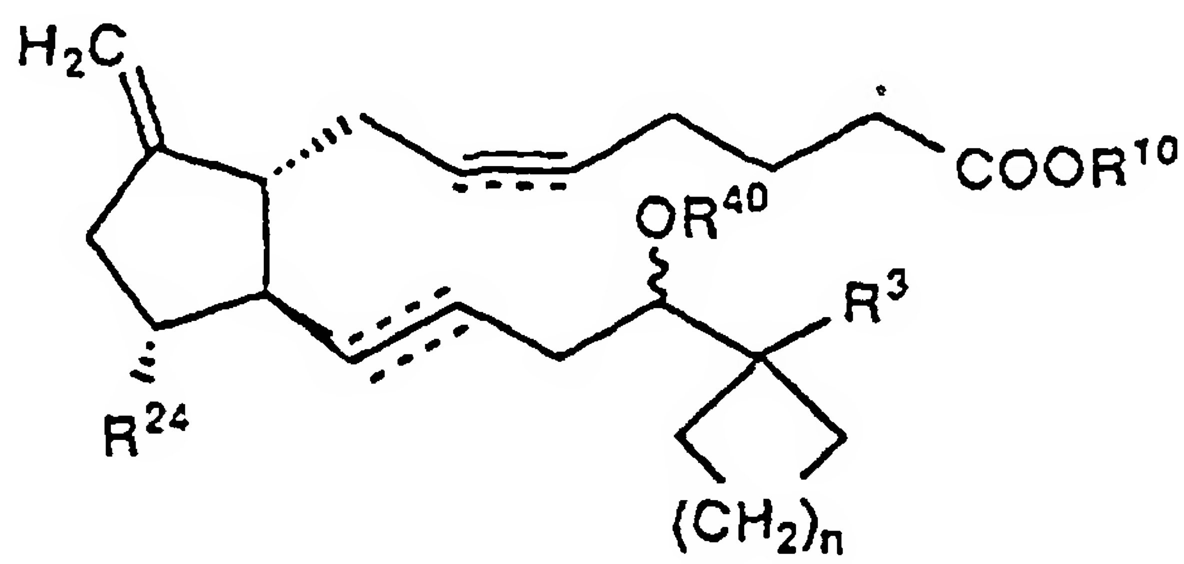
1) R^1 is oxo, R^{21} is hydroxy protecting group which may be eliminated under acidic conditions, i.e., the compound of formula (IIIA)



(IIIA)

wherein R^{24} is hydroxy protecting group which may be eliminated under acidic conditions, and the other symbols are as hereinbefore defined,

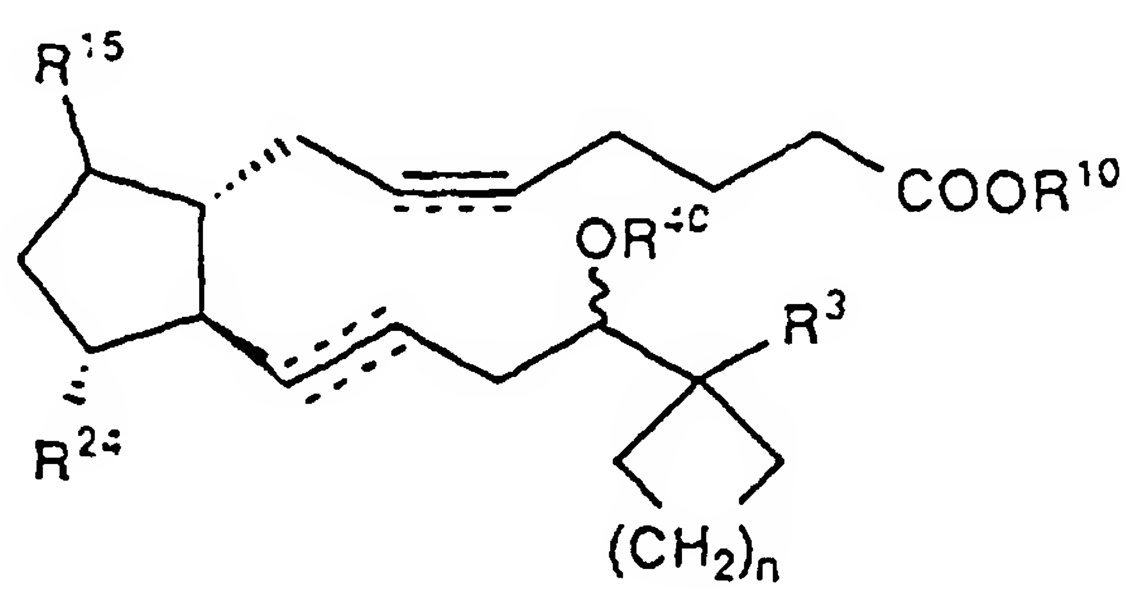
2) R^1 is methylene, R^{21} is hydroxy protecting group which may be eliminated under acidic conditions, i.e., the compound of formula (IIIB)



(IIIB)

wherein all symbols are as hereinbefore defined,

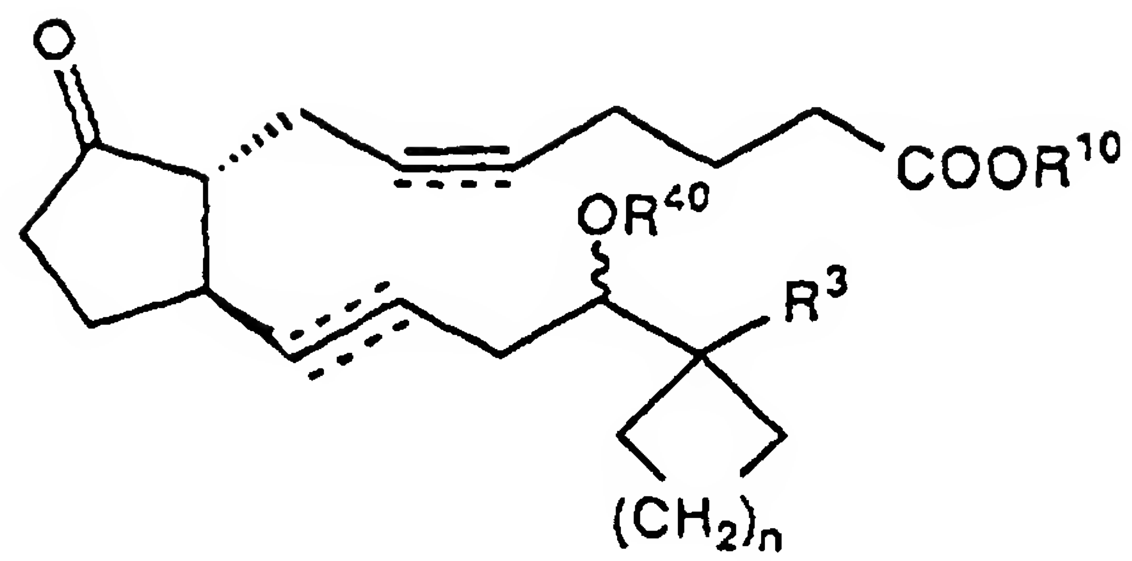
3) R^1 is halogen atom, R^{24} is hydroxy protecting group which may be eliminated under acidic conditions, i.e., the compound of formula (IIIC)



(IIIC)

wherein R^{15} is halogen atom and the other symbols are as hereinbefore defined,

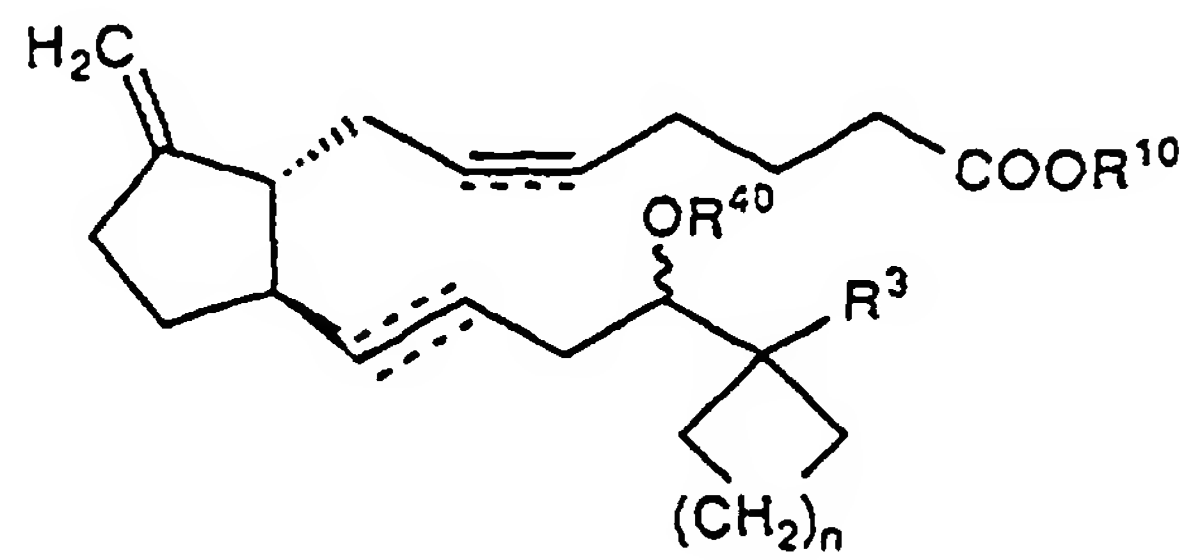
4) R^1 is oxo, R^{21} is hydrogen atom, i.e., the compound of formula (IIID)



(IIID)

wherein all symbols are as hereinbefore defined,

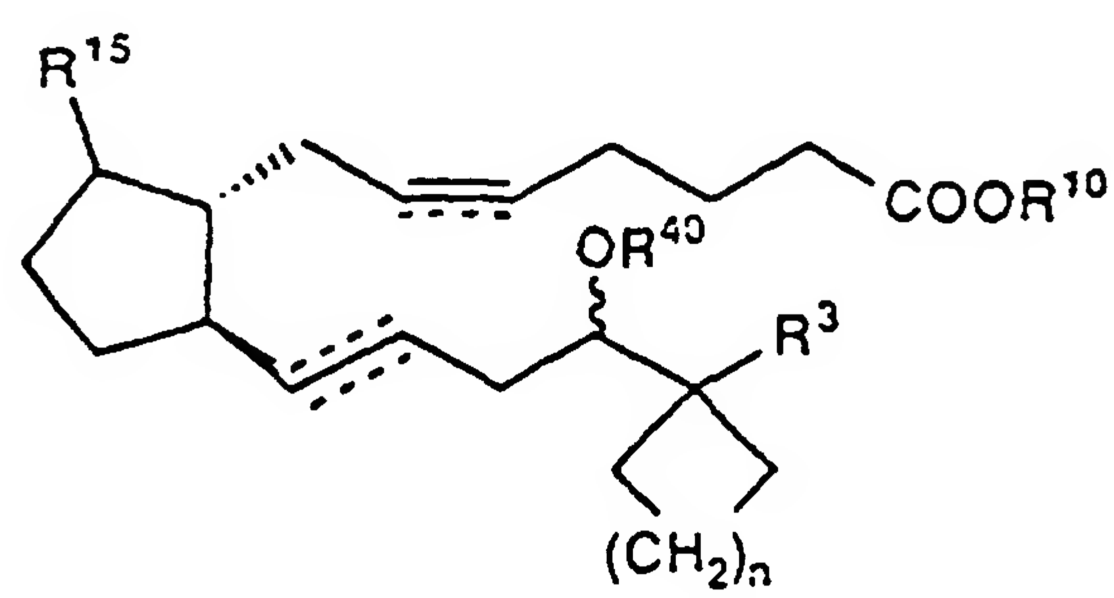
5) R^1 is methylene, R^{21} is hydrogen atom, i.e., the compound of formula (IIIE)



(IIIE)

wherein all symbols are as hereinbefore defined,

6) R^1 is halogen atom, R^{21} is hydrogen atom, i.e., the compound of formula (IIIF)



(IIIF)

wherein all symbols are as hereinbefore defined.

[0043] The compound of the formula (IIIB) may be prepared from the compound of the formula (IIIA) according to the reaction of the following Scheme (A).

[0044] The compound of the formula (IIIC) may be prepared from the compound of the formula (IIIA) according to the reaction of the following Scheme (B), (C) or (D).

[0045] The compound of the formula (IIID) may be prepared from the compound of the formula (IIIA) according to the reaction of the following Scheme (E).

[0046] The compound of the formula (IIIE) may be prepared from the compound of the formula (IIID) according to the same reaction of the following Scheme (A).

[0047] The compound of the formula (IIIF) may be prepared from the compound of the formula (IIID) according to

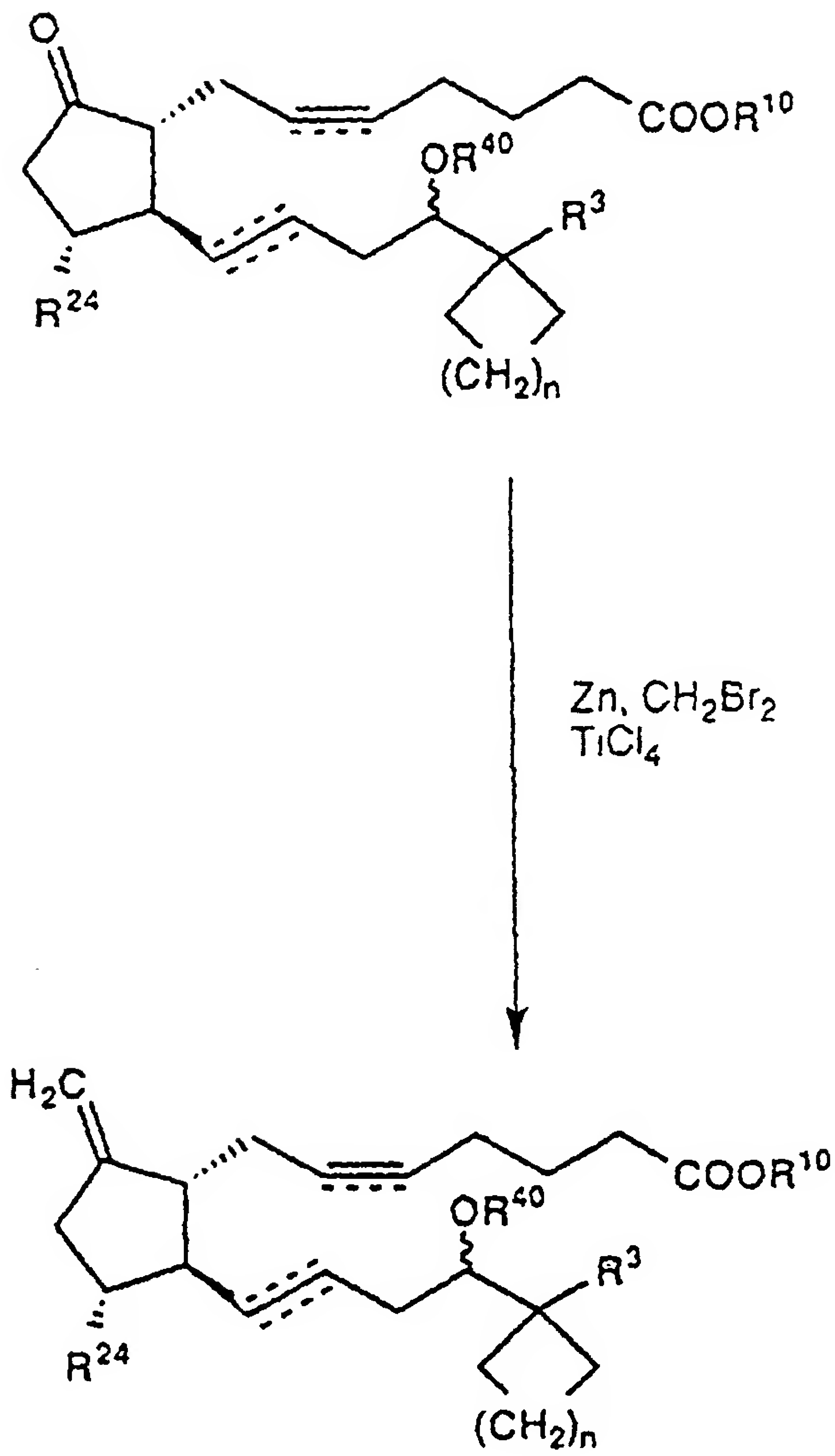
the same reaction of the following Scheme (B), (C) or (D).

[0048] The compound of the formula (IIIA) may be prepared according to the reaction of the following Scheme (F), (G) or (H)

[0049] In the Scheme, the symbols represent the following meanings or are as hereinbefore defined.

Ts is p-toluenesulfonyl;
Ac is acetyl;
Ph is phenyl;
AIBN is 2,2'-azobisisobutyronitrile;
DIBAL is diisobutylaluminum hydride;
t-Bu ist-butyl;
n-Bu is normal butyl;
c-Hex is cyclohexyl;
Et is ethyl;
EE is ethoxyethyl;
D-(-)-DIPT is D-(-)-diisopropyl tartarate;
L-(+)-DIPT is L-(+)-diisopropyl tartarate;
$Ti(OiPr)_4$ is titanium (IV) isopropoxide;
TBHP is t-butylhydroperoxide;
Cp_2ZrClH is bis(cyclopentadienyl)zirconium chloride hydride.

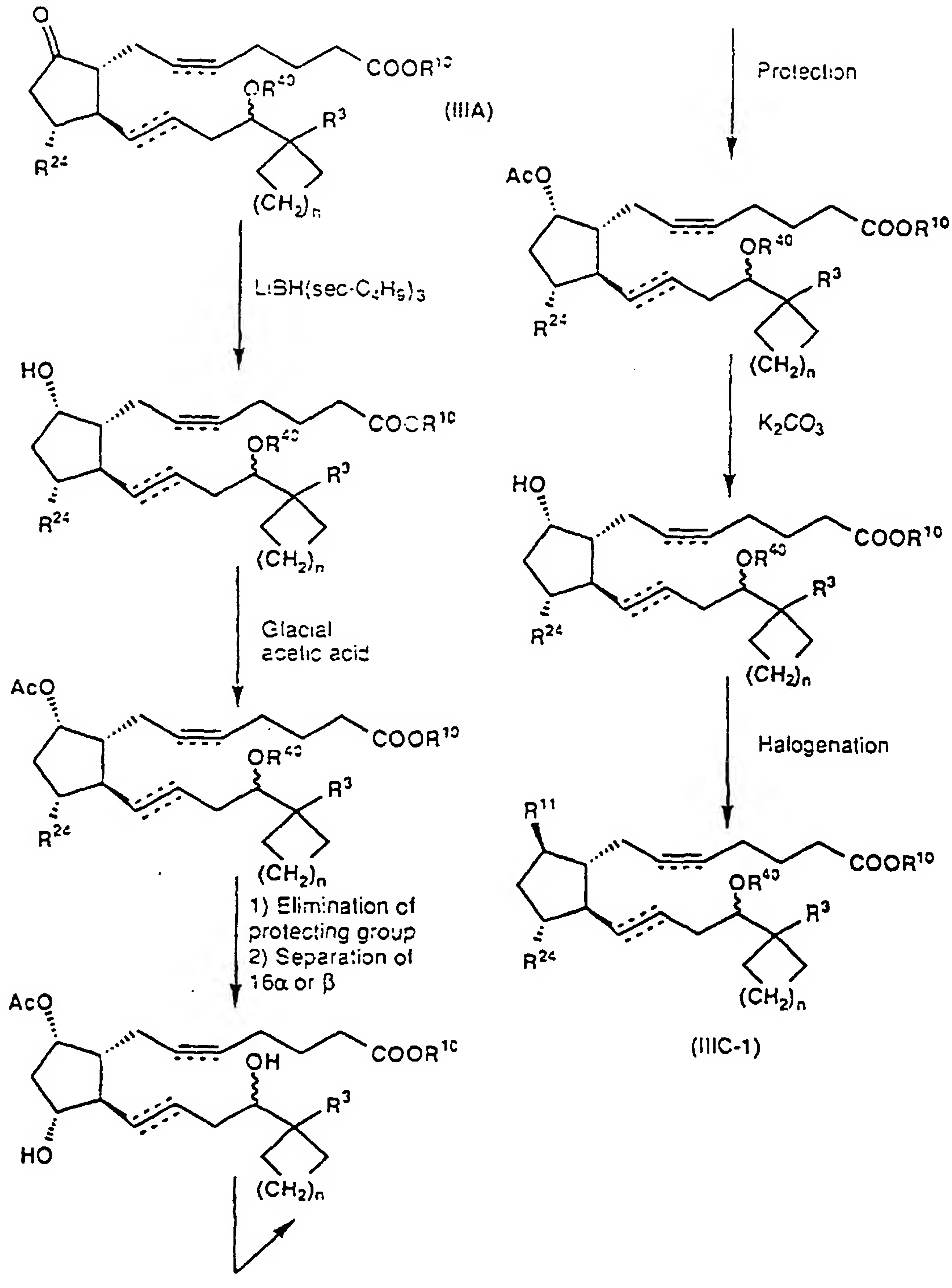
Scheme (A)



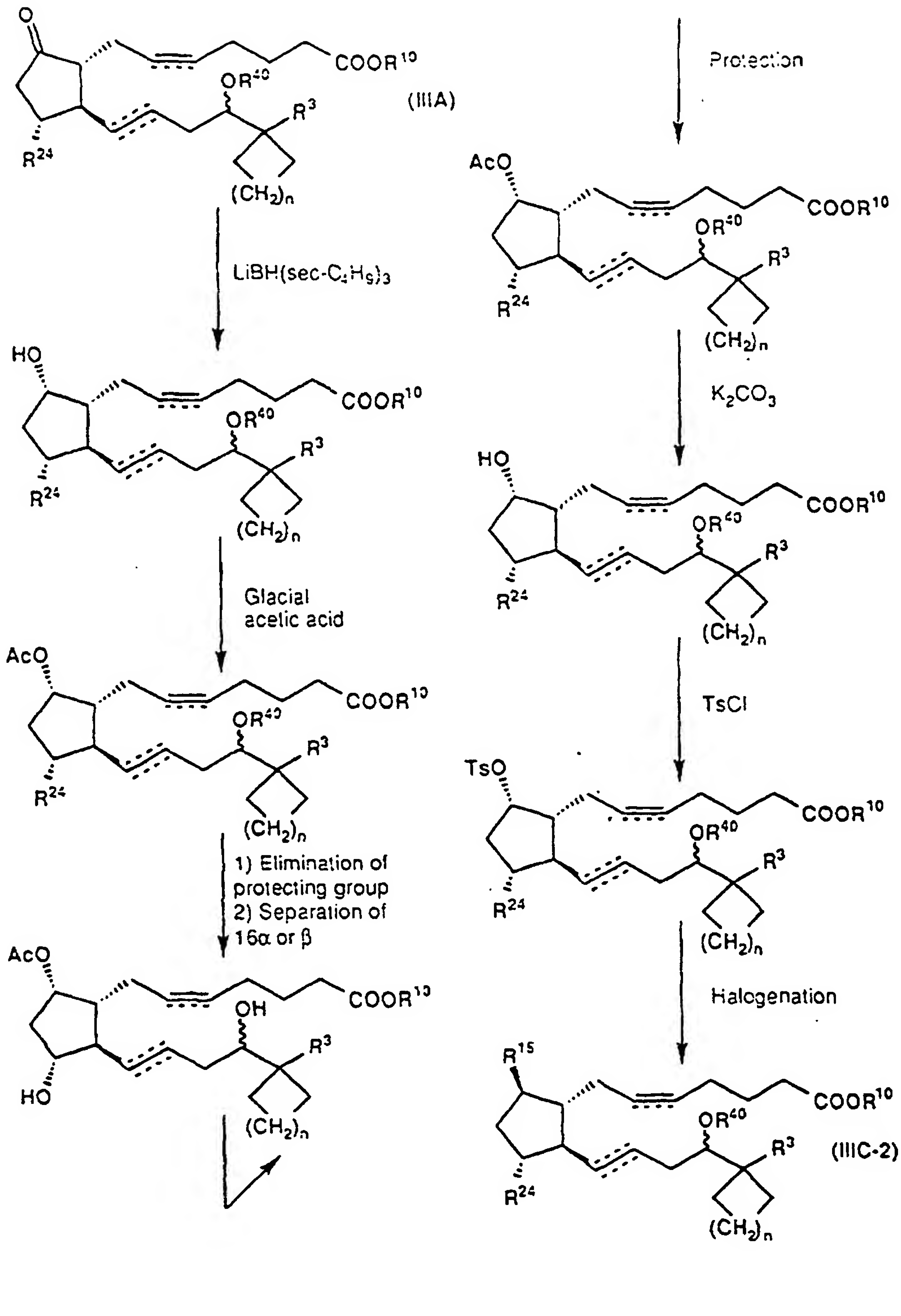
(IIIA)

(IIIB)

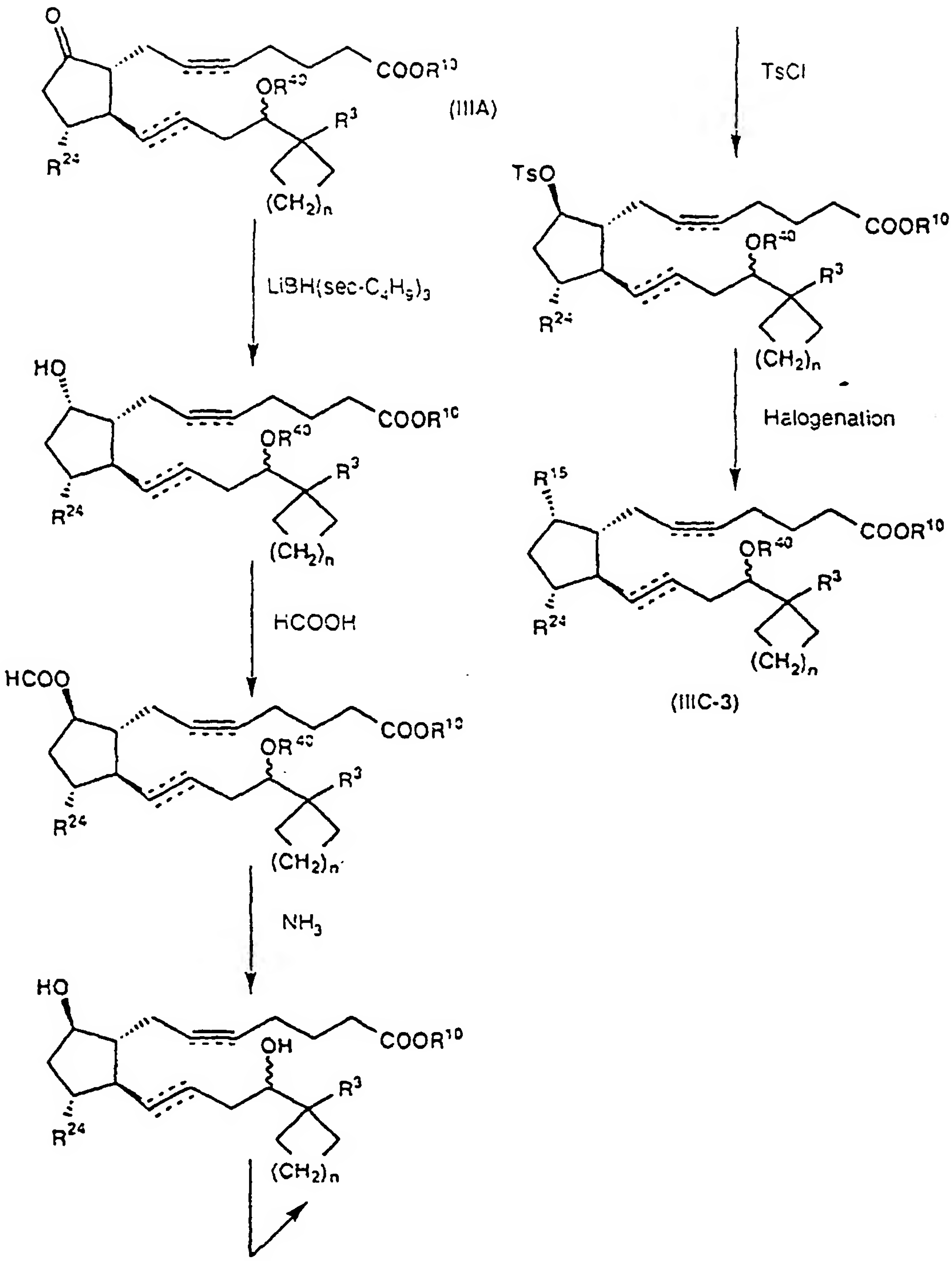
Scheme (B)


COOR10
OR40
R3
R24
(CH2)n
(IIIA)
LiBH(sec-C4H9)3
HO
AcO
Glacial acetic acid
1) Elimination of protecting group
2) Separation of 16α or β
OH
Protection
K2CO3
Halogenation
R11
(IIIC-1)

Scheme (C)

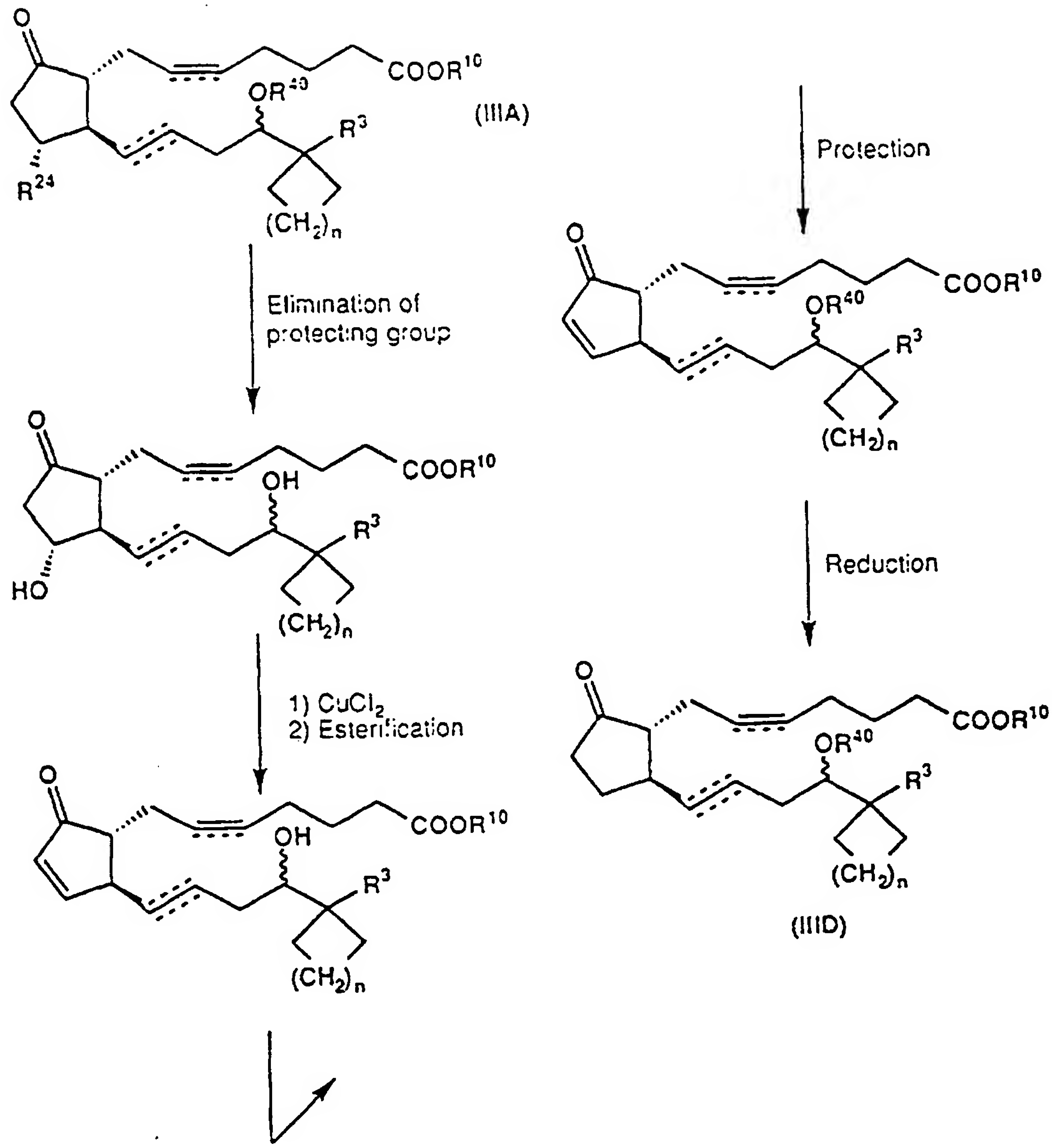

COOR10
OR40
R3
(IIIA)
R24
(CH2)n
LiBH(sec-C4H9)3
HO
Glacial
acetic acid
AcO
1) Elimination of
protecting group
2) Separation of
16α or β
OH
Protection
K2CO3
TsCl
TsO
Halogenation
R15
(IIIC-2)

Scheme (D)



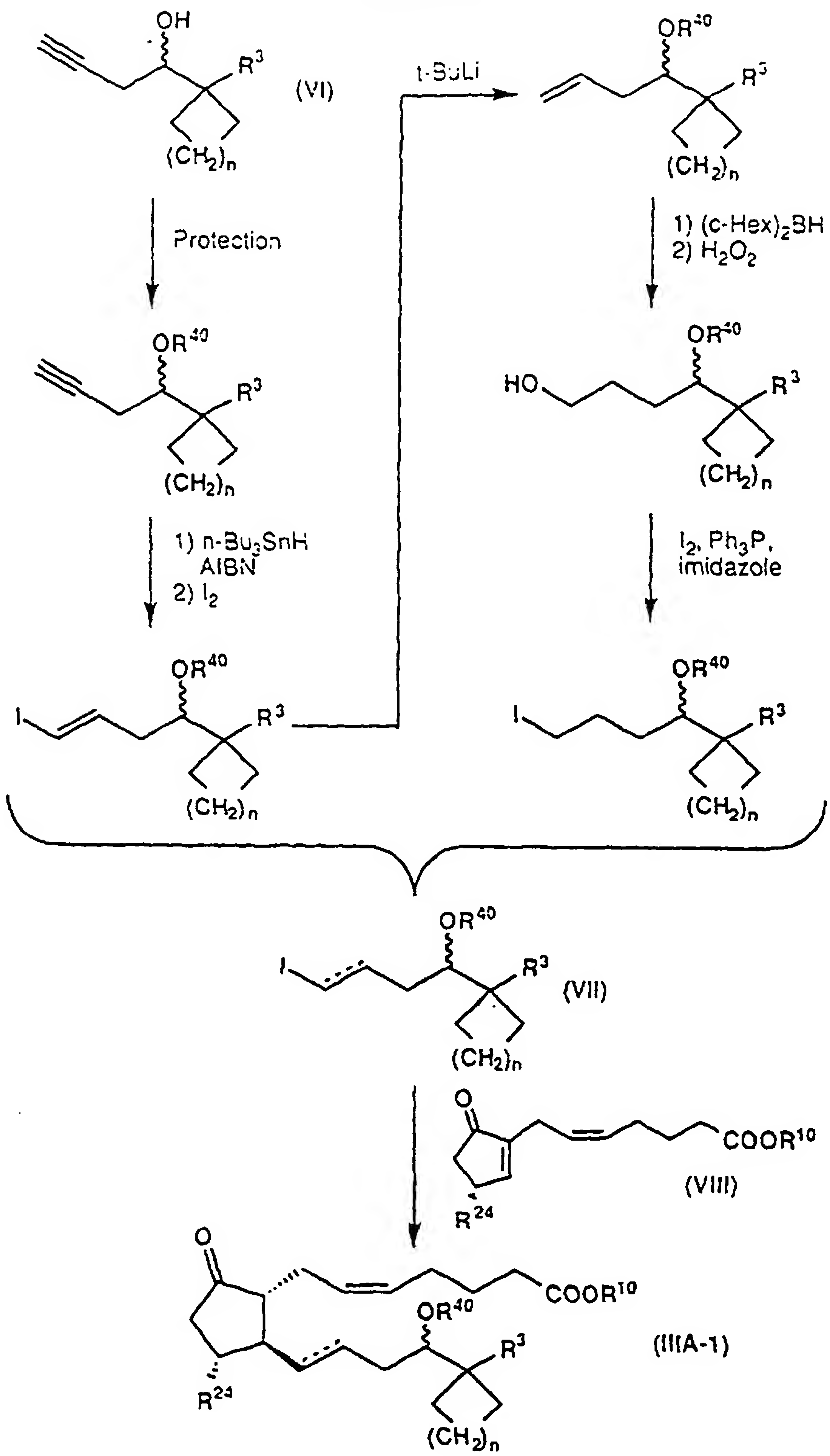
(IIIC-3)

Scheme (E)



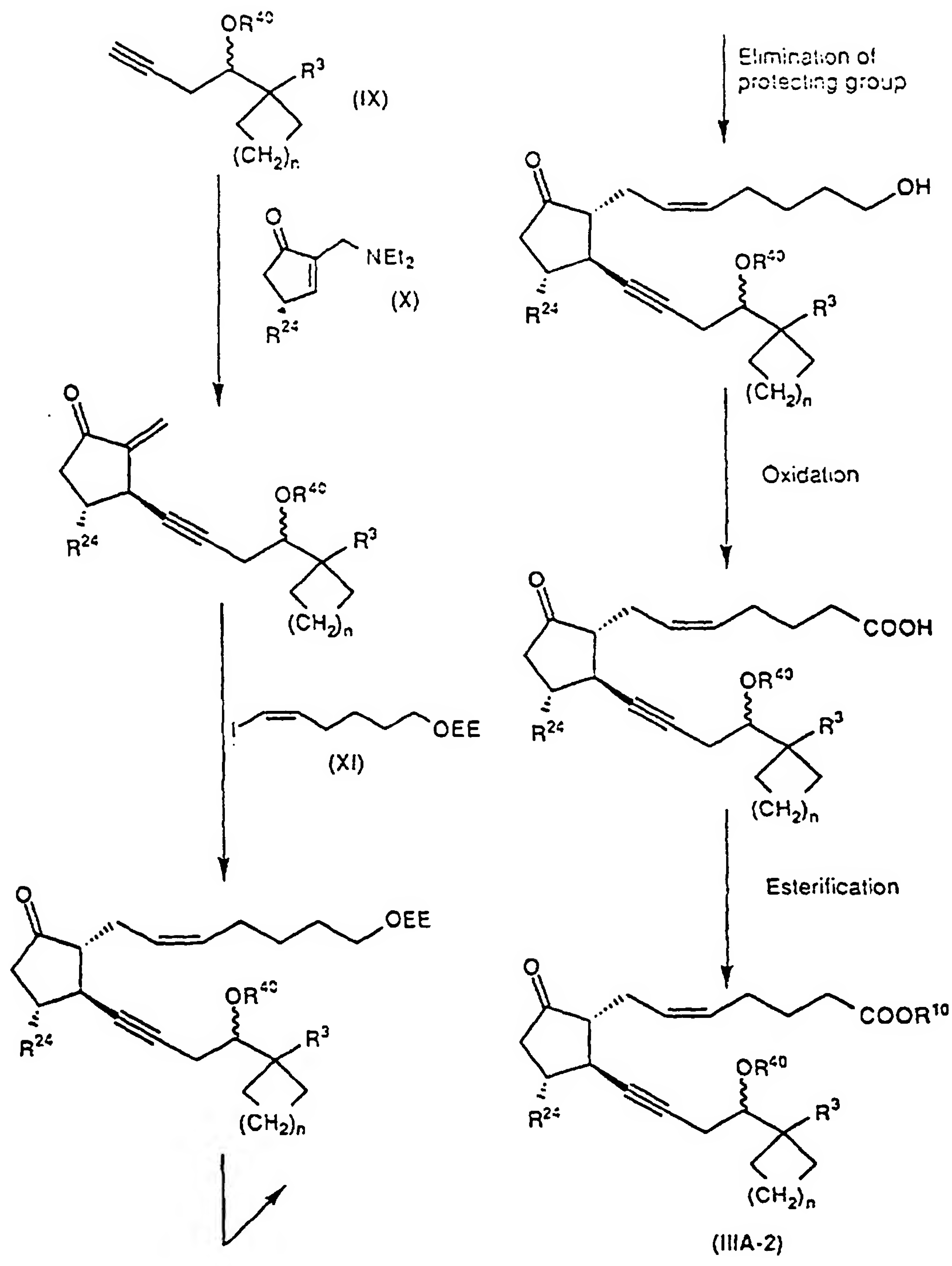
O
COOR10
OR40
(IIIA)
R3
R24
(CH2)n
Protection
Elimination of protecting group
OH
HO
1) CuCl2
2) Esterification
Reduction
(IIID)

Scheme (F)

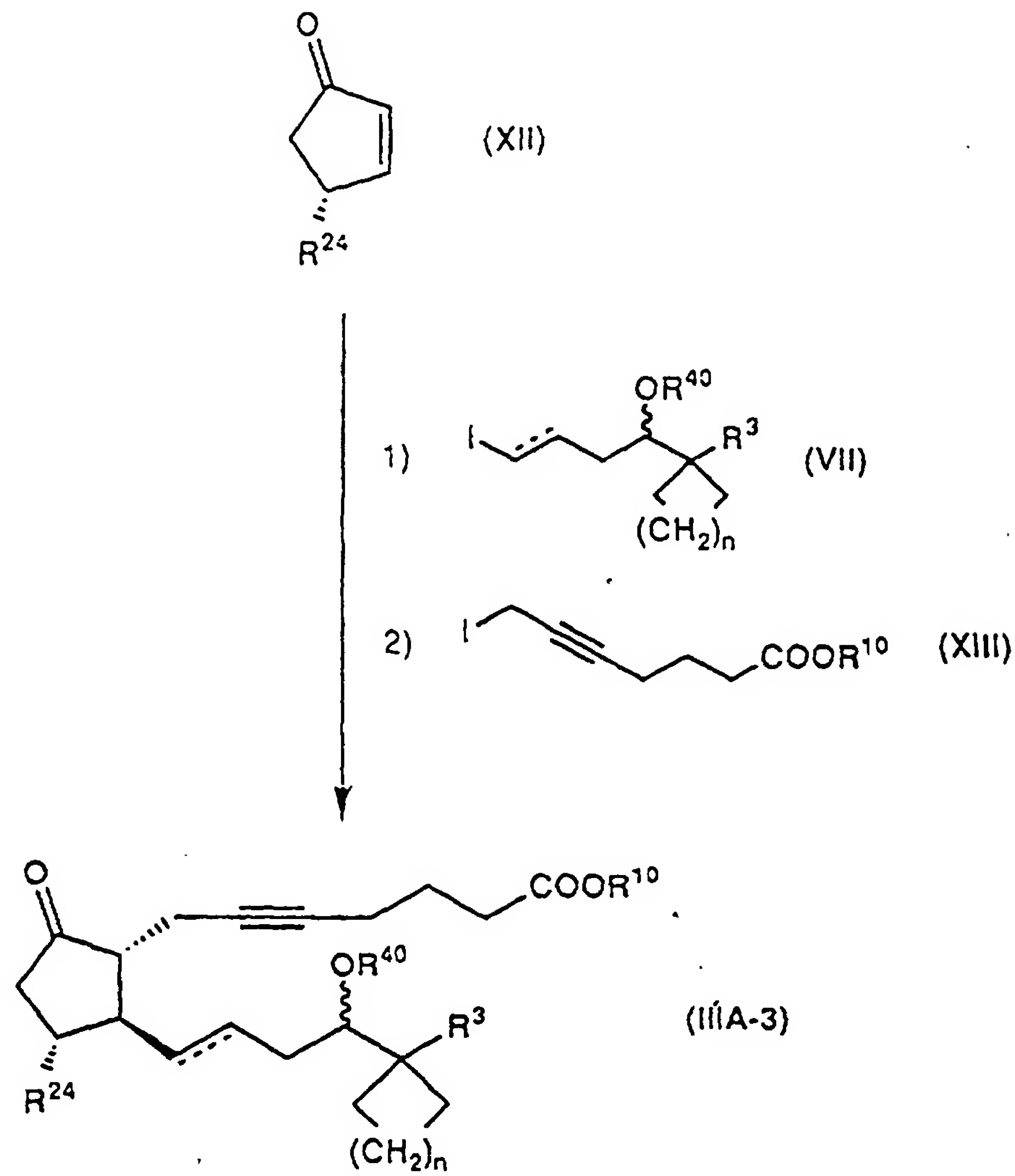


OH
R^3
(VI)
$(CH_2)_n$
Protection
OR^{40}
1) n-Bu_3SnH
AIBN
2) I_2
I
t-BuLi
1) $(c\text{-}Hex)_2BH$
2) H_2O_2
HO
I_2, Ph_3P,
imidazole
(VII)
O
$COOR^{10}$
(VIII)
R^{24}
(IIIA-1)

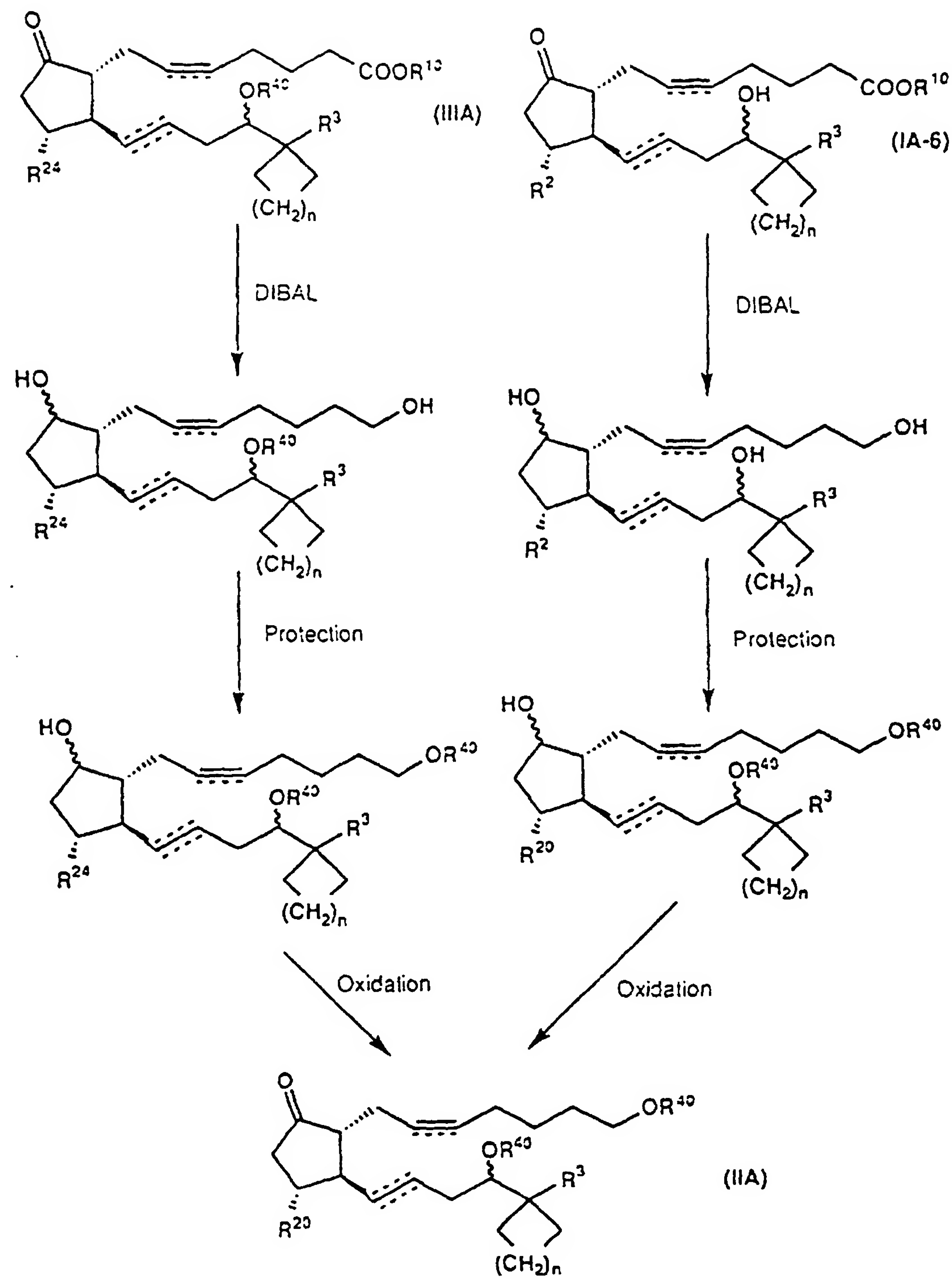
Scheme (G)


OR40
R3
(IX)
(CH2)n
NEt2
(X)
R24
I
OEE
(XI)
Elimination of protecting group
OH
Oxidation
COOH
Esterification
COOR10
(IIIA-2)

Scheme (H)

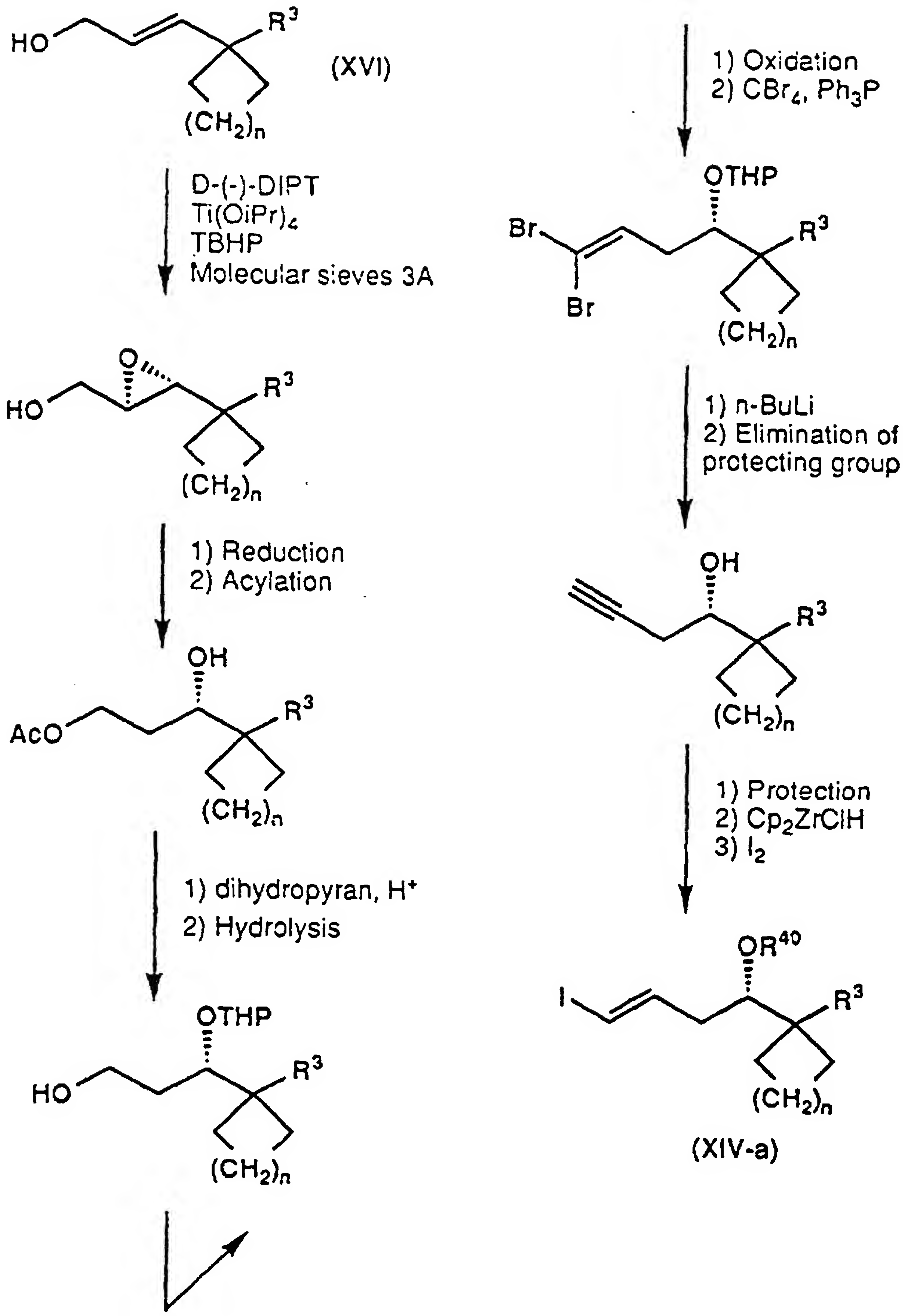


Scheme (J)

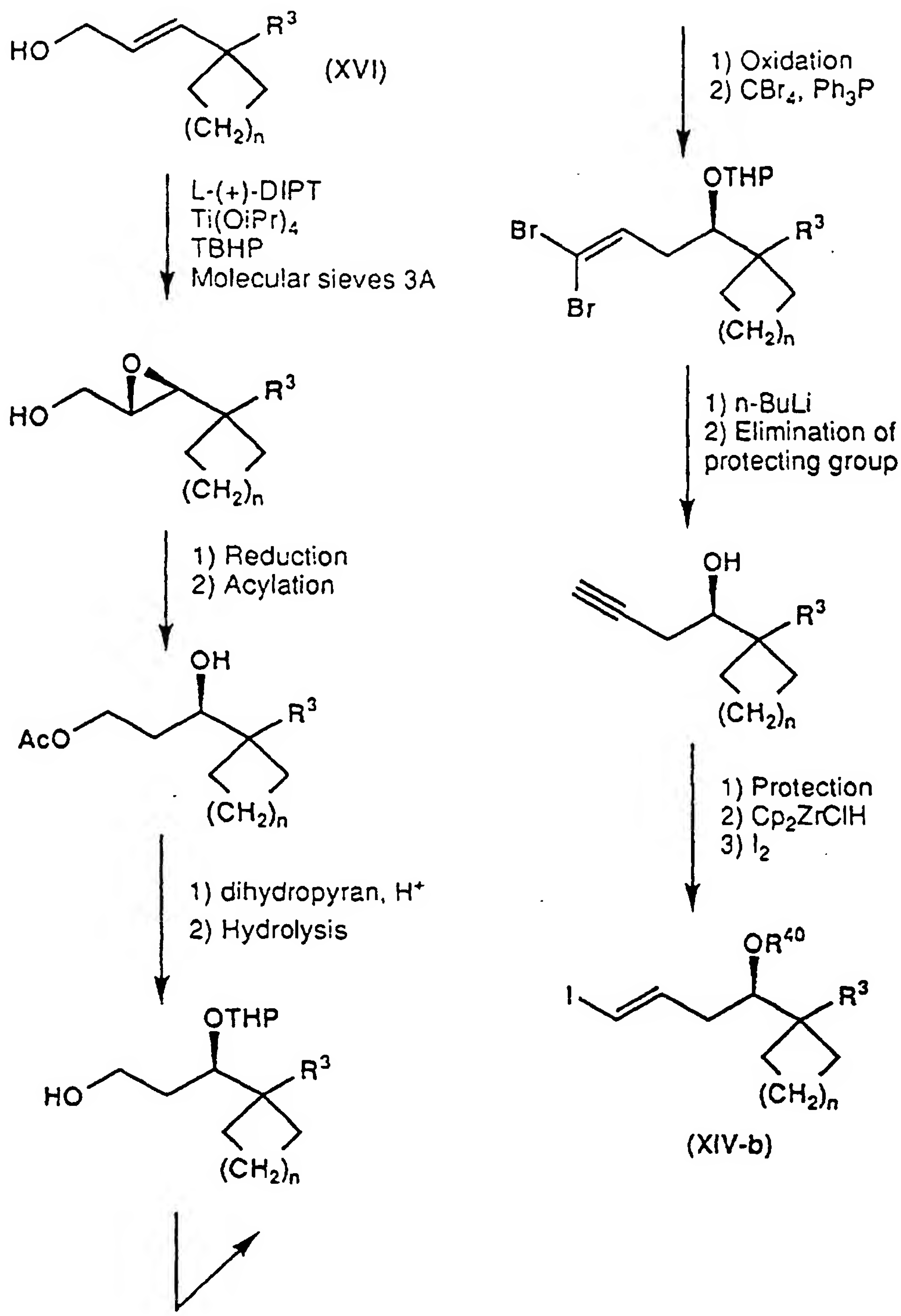


COOR[10]
OR[40]
R[3]
(IIIA)
R[24]
(CH2)n
OH
(IA-6)
R[2]
DIBAL
HO
OH
Protection
OR[40]
R[20]
Oxidation
(IIA)

Scheme (L)

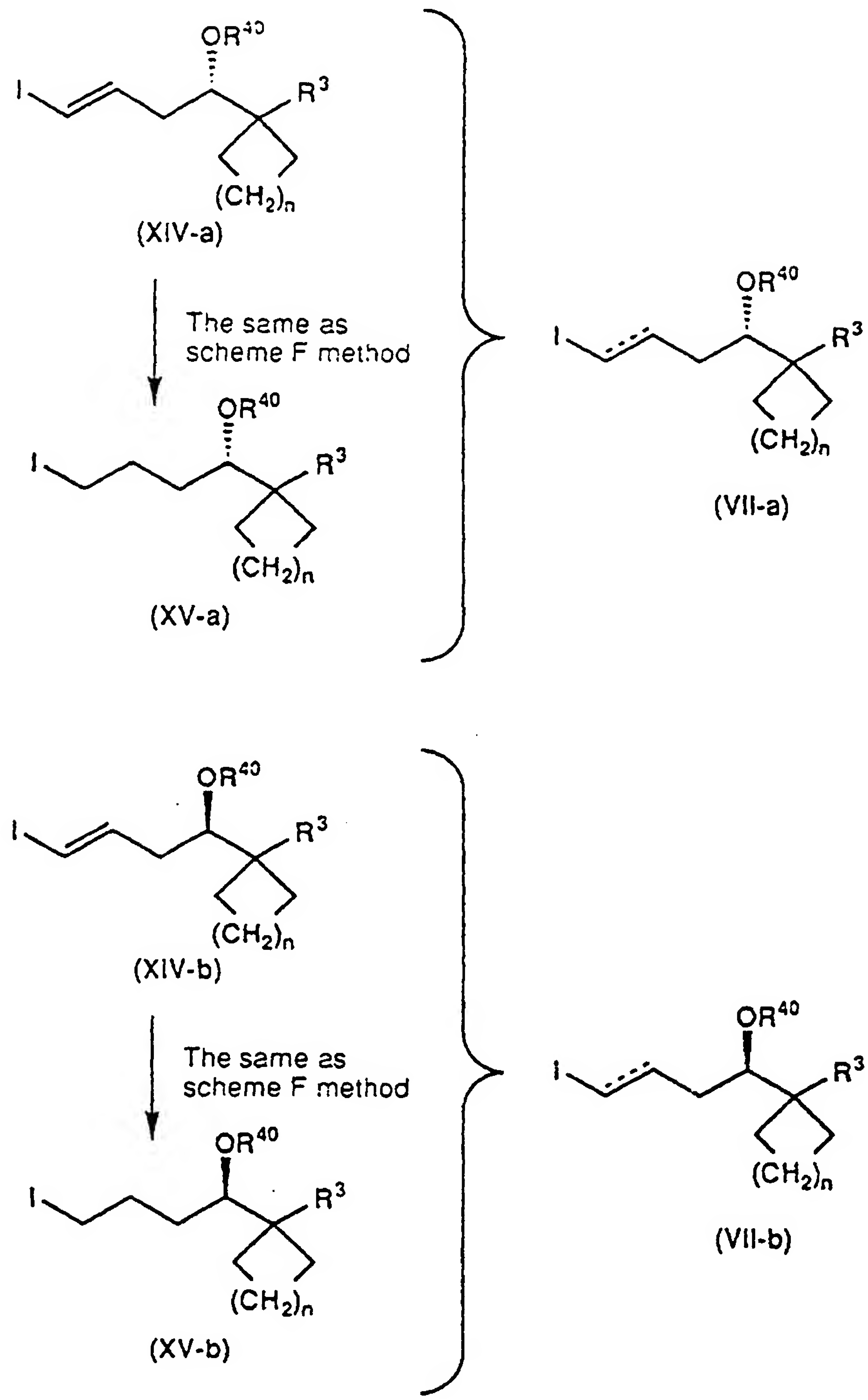

HO
R3
(XVI)
(CH2)n
D-(-)-DIPT
Ti(OiPr)4
TBHP
Molecular sieves 3A
O
HO
R3
(CH2)n
1) Reduction
2) Acylation
OH
AcO
R3
(CH2)n
1) dihydropyran, H+
2) Hydrolysis
OTHP
HO
R3
(CH2)n
1) Oxidation
2) CBr4, Ph3P
OTHP
Br
Br
R3
(CH2)n
1) n-BuLi
2) Elimination of
protecting group
OH
R3
(CH2)n
1) Protection
2) Cp2ZrClH
3) I2
OR40
I
R3
(CH2)n
(XIV-a)

Scheme (M)



(XIV-b)

Scheme (N)


OR40
I
R3
(CH2)n
(XIV-a)
The same as
scheme F method
OR40
I
R3
(CH2)n
(XV-a)
OR40
I
R3
(CH2)n
(VII-a)
OR40
I
R3
(CH2)n
(XIV-b)
The same as
scheme F method
OR40
I
R3
(CH2)n
(XV-b)
OR40
I
R3
(CH2)n
(VII-b)

[0050] Each reaction of hereinbefore described reaction Schemes may be carried out by known methods. In the reaction Schemes, the compounds of formula (VI), (VIII), (X), (XII), (XIII), (XI) and (XVI) as starting materials are known per se or may be prepared by known methods.

[0051] For example, in the compound of formula (VI), (4RS)-5,5-propanooct-1-yn-4-ol is known compound described in the specification of United States Patent No. 4132738.

[0052] In the compound of formula (VIII), (5Z)-7-((3R)-3-t-butyldimethylsilyloxy-5-oxocyclopent-1-ene)hept-5-enoic acid methylester and in the compound of formula (X), (4R)-2-(diethylaminomethyl)-4-t-butyldimethylsilyloxy-2-cyclopenten-1-one is known compound described in the literature of J. Org. Chem., 53, 5590-5592 (1988).

[0053] In the compound of formula (XII), (4R)-4-t-butyldimethylsilyloxy-2-cyclopenten-1-one and in the compound of formula (XIII), 7-iodohept-5-ynoic acid methylester is known compound described in the literature of J. Am. Chem. Soc., 110, No. 14, 4718-4726 (1988).

[0054] The compound of formula (XI) is known compound described in the literature of J. Am. Chem. Soc., 97, 4745-4746 (1975).

[0055] The starting materials and reagents in the present invention are known per se or may be prepared by known methods.

[0056] In each reaction in the present specification, obtained products may be purified by conventional techniques. For example, purification may be carried out by distillation at atmospheric or reduced pressure, by high performance liquid chromatography, by thin layer chromatography or by column chromatography using silica gel or magnesium silicate, by washing or by recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

Pharmacological Activities

[0057] The compounds of the present invention of the formula (I) bind and act on EP_2 receptor which is a subtype of of PGE_2 receptor.

[0058] For example, in standard laboratory test, the effects of the compounds of the present invention were confirmed by binding assay using expression cell of prostanoide receptor subtype.

Binding assay using expression cell of prostanoide receptor subtype

[0059] The preparation of membrane fraction was carried out according to the method of Sugimoto et. al. [J. Biol. Chem. 267, 6463-6466 (1992)], using expression CHO cell of the prostanoide receptor subtype (mouse EP_1, EP_2, $EP_{3\alpha}$, EP_4).

[0060] The standard assay mixture containing membrane fraction (0.5 mg/ml), and [^{3}H]-PGE_2 in a final volume of 200 μl was incubated for 1 hour at room temperature. The reaction was terminated by the addition of 3 ml of ice-cold buffer. The mixture was rapidly filtered through a GF/B glass filter. The radioactivity associated with the filter was measured by liquid scintillation counting.

[0061] Kd and Bmax values were determined from Scatchard plots [Ann. N.Y. Acad. Sci., 51, 660 (1949)]. Non-specific binding was calculated as the binding in the presence of an excess (2.5 μM) of unlabeled PGE_2. In the experiment for competition of specific ^{3}H-PGE2 binding by the compounds of the present invention, 2.5 nM of ^{3}H-PGE2 and various concentrations of compounds of the present invention were added. The following buffer was used in all reactions.

[0062] Buffer : 10 mM potassium phosphate (pH 6.0), 1 mM EDTA, 10 mM $MgCl_2$, 0.1M NaCl

[0063] All of the values shown are those obtained using the more polar stereoisomer of the exemplified compounds.

[0064] The dissociation constant (Ki) of each compound was calculated by the following equation.

$$Ki = IC_{50}/(1+([C]/Kd))$$

[0065] The results are shown in Table 15.

[Table 15]

Example No.	Ki (μM)			
	EP_1	EP_2	$EP_{3\alpha}$	EP_4
4	>10	0.092	>10	>10
4(5)	>10	0.032	>10	>10

[Table 15] (continued)

Example No.	Ki (μM)			
	EP_1	EP_2	$EP_{3\alpha}$	EP_4
4(10)	>10	0.030	>10	>10
6(1)	>10	0.036	>10	>10
6(5)	>10	0.076	>10	>10
10	>10	0.034	>10	>10
12	>10	0.37	>10	>10
16(1)	>10	0.096	>10	>10
17(2)	1.10	0.0009	2.70	0.40

Toxicity

[0066] The toxicity of the compounds of the present invention is very low and therefore, it is confirmed that these compounds are safe for pharmaceutical use.

Application for Pharmaceuticals

[0067] The compounds of the present invention of the formula (I) bind strongly and act on PGE_2 receptor, especially on EP_2 subtype receptor and therefore are useful for prevention and/or treatment of immunological diseases (autoimmune diseases, organ transplantation, etc.), asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma etc.

[0068] Among the compounds of the present invention of the formula (I), compounds which bind weakly on to receptor subtypes except for EP_2 receptors and other arachidonic acid metabolism receptors (thromboxane receptor, PGI_2 receptor, etc.) do not express other effects and therefore it is thought that such compounds will be a medical agent which have less side-effects.

[0069] For the purpose above described, the compounds of the formula (I), (IA), (IB) and (IC), prodrugs thereof, non-toxic salts thereof and cyclodextrin clathrates thereof may be normally administered systemically or partially, usually by oral or parenteral administration. To convert prodrug, they have merit of non-stimulant, good-absorbability, good-solubility, etc.

[0070] The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person per dose are generally from 1 μg to 100 mg, by oral administration, up to several times per day, and from 0.1 μg to 10 mg, by parenteral administration (preferred into vein) up to several times per day, or continuous administration for from 1 to 24 hrs. per day into vein.

[0071] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0072] The compounds of the present invention may be administered in the form of, for example, solid compositions, liquid compositions or other compositions for oral administration,or injections, liniments or suppositories etc. for parenteral administration.

[0073] Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules.

[0074] Capsules include hard capsules and soft capsules.

[0075] In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent such as lactose, mannitol, mannit, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate. The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents such as magnesium stearate, disintegrating agents such as cellulose calcium glycolate, and assisting agents for dissolving such as glutamic acid, asparaginic acid. The tablets or pills may, if desired, be coated with film of gastric or enteric material such as sugar, gelatin, hydroxypropyl cellulose cr hydroxypropyl cellulose phthalate etc., or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

[0076] Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, syrups and elixirs etc. In such liquid compositions, one or more of the active compound(s) is or are comprised in inert diluent (s) commonly used in the art (for example, purified water, ethanol etc.). Besides inert diluents, such compositions may also comprise adjuvants such as wetting agents, suspending agents, sweetening agents, flavouring agents, perfuming

agents and preserving agents.

[0077] Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents such as sodium hydrogen sulfate, stabilizing agents to give isotonicity, isotonic buffer such as sodium chloride, sodium citrate, citric acid. For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.

[0078] Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Aqueous solutions or suspensions include distilled water for injection and physiological salt solution. Non-aqueous solutions or suspensions include propylene glycol, polyethylene glycol, plant oil such as olive oil, alcohol such as ethanol, POLYSORBATE80 (registered trade mark) etc. Such compositions may comprise additional diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent, assisting agents such as assisting agents for dissolving (for example, glutamic acid, asparaginic acid). They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactured in the form of sterile solid compositions and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

[0079] Other compositions for parenteral administration include liquids for external use, and endemic liniments, ointment, suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

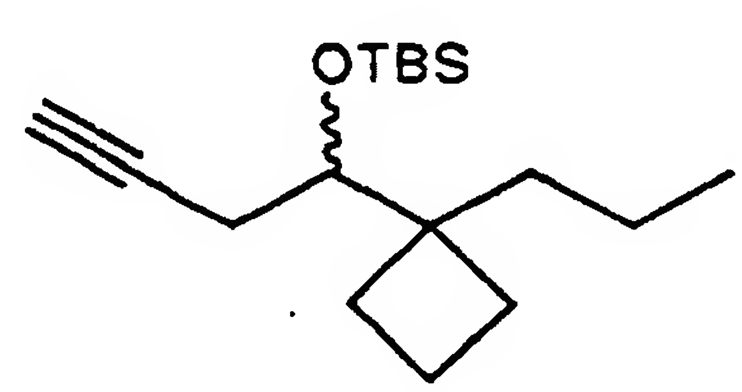
Reference examples and Examples

[0080] The following reference examples and examples are intended to illustrate the present invention. The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations. NMR in the parentheses show measured solvents. In the example, TBS is t-butyldimethylsilyl, THP is tetrahydropyranyl, Ac is acetyl, EE is ethoxyethyl.

Reference example 1

(4RS)-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-yne

[0081]



[0082] To the mixture solution of (4RS)-5,5-propanoocta-1-yne-4-ol (4.0 g) and imidazole (4.9 g) in dimethylformamide (50 ml) was added t-butyldimethylsilylchloride (5.4 g) under cooling with ice. The reaction mixture was stirred at 60 °C for 7 hours. The reaction mixture was quenched by addition of water, extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane → hexane : ethyl acetate = 10: 1) to give the title compound (6.8 g) having the following physical data.

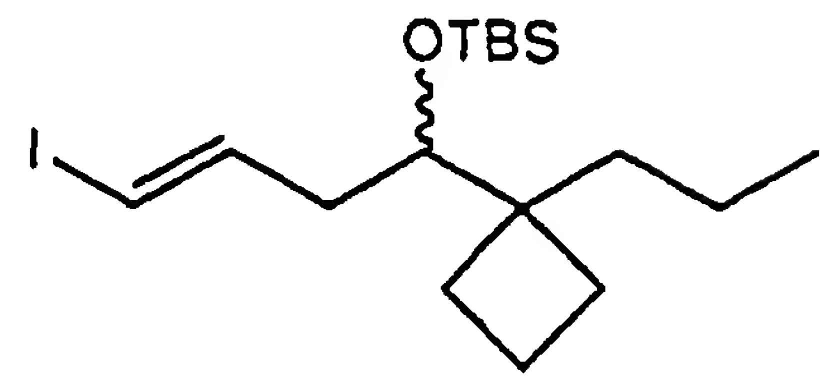
TLC: Rf 0.64 (hexane);

NMR ($CDCl_3$) : δ 3.75 (1H, t, J=5.8 Hz), 2.28 (1H, ddd, J=17, 5.0, 2.5 Hz), 2.16 (1H, ddd, J=17. 6.0, 2.5 Hz), 2.10-1.94 (1 H, m), 1.92 (1H, t, J=2.5 Hz), 1.90-1.20 (9H, m), 0.90 (3H, t, J=6.0 Hz), 0.89 (9H, s), 0.12 (3H, s), 0.07 (3H, s).

Reference example 2

(1E,4RS)-1-iodo-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-ene

[0083]



[0084] To the mixture of the compound prepared in reference example 1 (3.0 g) and tributyltinhydride (3.7 ml) was added azobisisobutyronitrile (35 mg). The mixture was stirred at 80 °C for 1.5 hours. After the mixture was cooled to room temperature, to the mixture was added dropwise iodine (4.1 g) in dichloromethane (70 ml). The reaction mixture was stirred for 10 min. To the reaction mixture was added a saturated aqueous solution of sodium thiosulfate, ethyl acetate and a saturated aqueous solution of sodium chloride, stirred, filtered, and extracted. The water layer was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane) to give the title compound (3.9 g) having the following physical data.

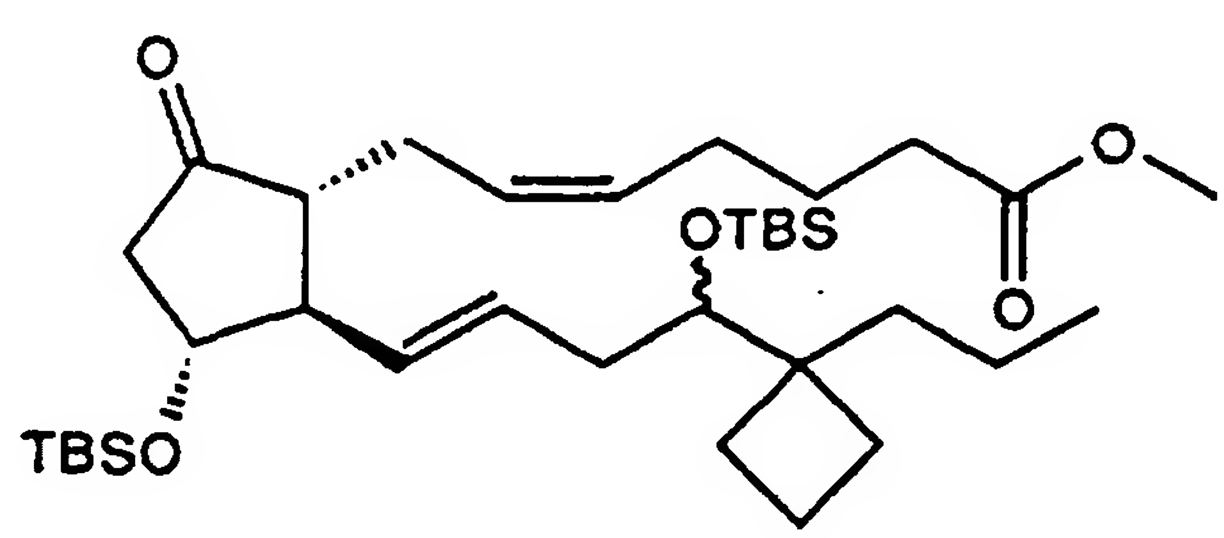
TLC: Rf 0.77 (hexane);

NMR ($CDCl_3$) : δ 6.49 (1H, dt, J=14.5, 7.5 Hz), 5.97 (1H, d, J=14.5 Hz), 3.58 (1H, t, J=6.0 Hz), 2.20-1.20 (12H, m), 0.91 (3H, t, J=6.0 Hz), 0.91 (9H, s), 0.06 (3H, s), 0.05 (3H, s).

Reference example 3

(5Z,11α,13E,16RS)-11,16-bis(t-butyldimethylsilyloxy)-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester

[0085]



[0086] To a solution of (1E,4RS)-1-iodo-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-ene (368 mg) in ether (6 ml) was added dropwise 1.7 M t-butyllithium in pentane solution (1.06 ml) at -78 °C. After the mixture was stirred for 45 min, to the mixture was added 0.25 M lithium 2-thienylcyanocuprate in tetrahydrofuran (4.33 ml). After the mixture was stirred for 20 min at same temperature, to the mixture was added dropwise a solution of (5Z)-7-((3R)-3-t-butyldimethylsilyloxy-5-oxocyclopenta-1-ene)hepta-5-enoic acid · methylester (290 mg) in ether (4 ml). The reaction mixture was warmed up to 0 °C for 1 hour. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of ammonium chloride and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 25 : 1) to give the title compound (332 mg) having the following physical data.

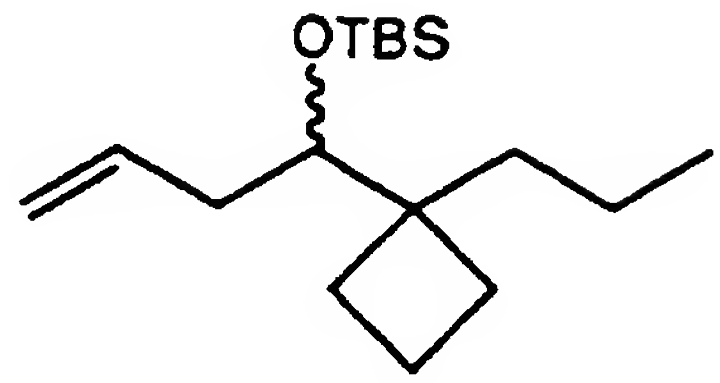
TLC: Rf 0.37 (hexane : ethyl acetate = 10:1);

NMR ($CDCl_3$) : δ 5.75-5.45 (1H, m), 5.45-5.20 (3H, m), 4.01 (1H, q, J=7.0 Hz), 3.66 (3H, s), 3.57 (1H, J=4.5 Hz), 2.60 (1H, dd, J=17.5, 6.5 Hz), 2.54-2.24 (3H, m), 2.30 (2H, t, J=7.0 Hz), 2.24-1.96 (6H, m), 1.96-1.20 (12H, m), 0.95 (3H, m), 0.91 (9H, s), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.03 (3H, s).

Reference example 4

(4RS)-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-ene

[0087]



[0088] To a solution of the compound prepared in reference example 2 (629 mg) in anhydrous ether (10 ml) was added dropwise 1.57 M t-butyllithium in pentane solution (1.96 ml) at -78 °C. The reaction mixture was stirred for 1 hour. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride (20 ml), extracted with hexane (x2). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane) to give the title compound (434 mg) having the following physical data.

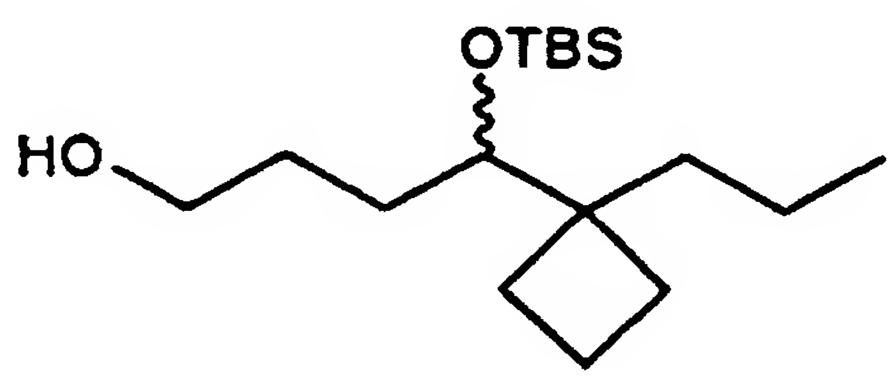
TLC: Rf 0.75 (hexane);

NMR ($CDCl_3$) : δ 5.83 (1H, ddt, J=17, 9.8, 7.4 Hz), 5.06-4.92 (2H, m), 3.59 (1H, dd, J=6.0, 4.6 Hz), 2.20-2.00 (2H, m), 2.00-1.20 (10H, m), 0.90 (3H, t, J=5.0 Hz), 0.83 (9H, s), 0.03 (6H, s).

Reference example 5

(4RS)-4-t-butyldimethylsilyloxy-5,5-propanooctan-1-ol

[0089]



[0090] To a borane-tetrahydrofuran complex (2.3 ml, 1.0 M tetrahydrofuran solution) was added dropwise cyclohexene (468 μl) at 0 °C under an atmosphere of argon. The mixture was stirred for 1.5 hours. To the mixture was added dropwise a solution of the compound prepared in reference example 4 (434 mg) in tetrahydrofuran (10 ml) at 0 °C. The reaction mixture was stirred for 30 min at same temperature, and stirred for 30 min at room temperature. To the reaction was added 1N aqueous solution of sodium hydroxide and 31% aqueous solution of hydrogen peroxide (3 ml). The mixture was stirred at room temperature 'or 30 min. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium thiosulfate (5 ml), extracted with ether. The extract was washed with a saturated aqueous solution of sodium thiosulfate and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane → ethyl acetate) to give the title compound (439 mg) having the following physical data.

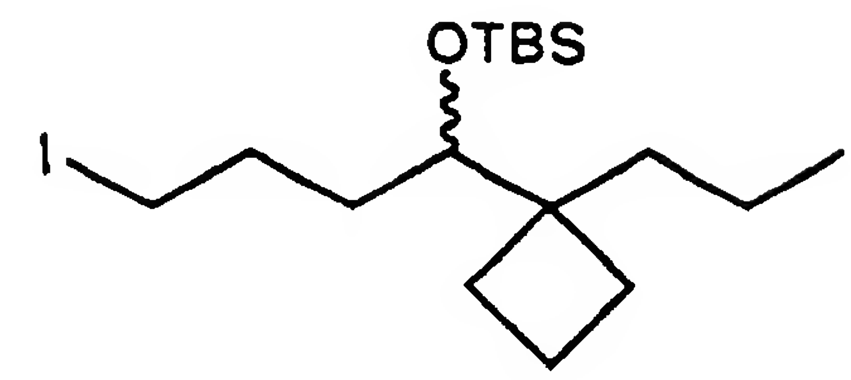
TLC: Rf 0.52 (hexane : ethyl acetate = 4 : 1);

NMR ($CDCl_3$) : δ 3.61 (2H, t, J=6.2 Hz), 3.55 (1H, t, J=4.6 Hz), 2.18-1.20 (14H, m), 0.95-0.85 (12H, m), 0.05 (6H, s).

Reference example 6

(4RS)-4-t-bulyldimethylsilyloxy-1-iodo-5,5-propanooctane

[0091]



[0092] To a solution of the compound prepared in reference example 5 (430 mg) in anhydrous benzene (10 ml) was successively added imidazole (243 mg), triphenylphosphine (936 mg) and iodine (726 mg). The reaction mixture was stirred for 15 min. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium thiosulfate, extracted with benzene (x2). The extract was washed with a saturated aqueous solution of sodium chloride (x2), dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane) to give the title compound (553 mg) having the following physical data.

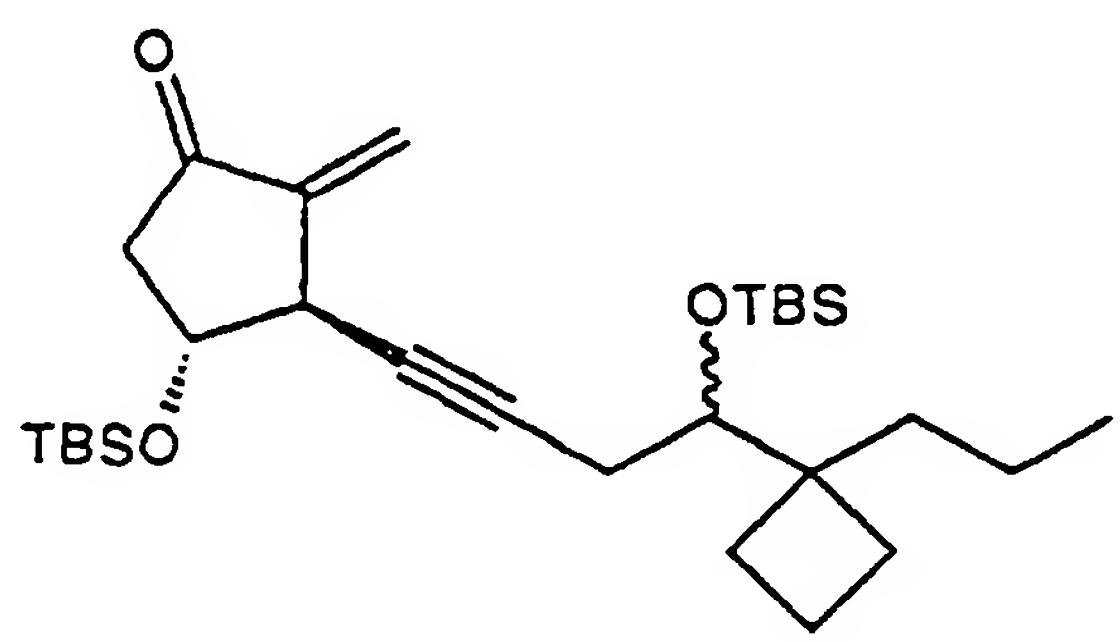
TLC: Rf 0.63 (hexane);

NMR ($CDCl_3$) : δ 3.54 (1H, t, J=5.0 Hz), 3.16 (2H, t, J=6.8 Hz), 2.17-1.22 (14H, m), 0.95-0.85 (12H, m), 0.09 (3H, s).

Reference example 7

(3R,4R)-4-t-butyldimethylsilyloxy-2-methyliden-3-((4RS)-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-yne-1-yl) cyclopentanone

[0093]



[0094] To a solution of (4RS)-t-butyldimethylsilyloxy-5,5-propanoocta-1-yne (730 mg) in toluene (5 ml) was added dropwise 1.6 M n-butyllithium in hexane solution (1.6 ml). After the mixture was stirred for 30 min, to the mixture was added dropwise 0.95 M diethylaluminum chloride in hexane solution (2.95 ml). After the mixture was stirred for 30 min, to the mixture was added dropwise a solution of (4R)-2-(diethylaminomethyl)-4-t-butyldimethylsilyloxy-2-cyclopenten-1-one (595 mg) in toluene (8 ml). The reaction mixture was stirred at room temperature for 15 min. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride and 2N aqueous solution of hydrochloric acid, extracted with hexane. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 100 : 1) to give the title compound (364 mg) having the following physical data.

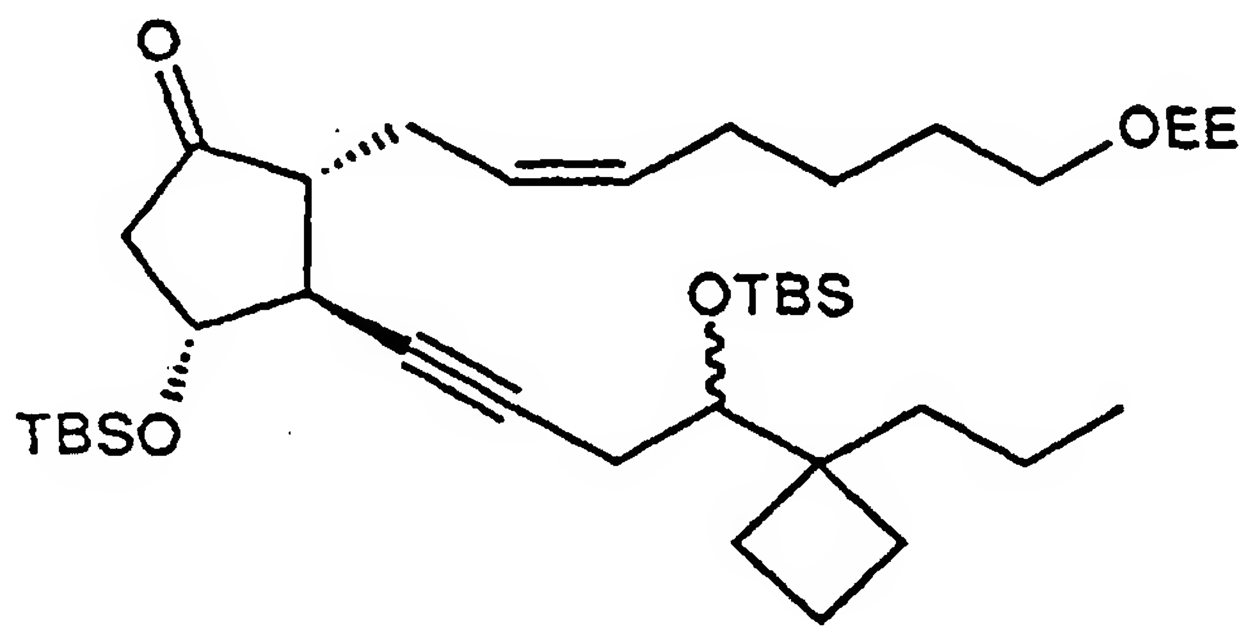
TLC: Rf 0.77(hexane : ethyl acetate = 10 : 1);

NMR ($CDCl_3$) : δ 6.12 (1H, d, J=3.0 Hz), 5.53 (1H, d. J=3.0 Hz), 4.25 (1H, m), 3.71 (1H t, J=5.3 Hz), 3.50-3.40 (1H, m), 2.70 (1H, dd, J=18.0, 6.4 Hz), 2.40-1.20 (13H, m), 0.95-0.82 (21H, m), 0.18-0.02 (12H, m).

Reference example 8

(2R,3R,4R)-4-t-butyldimethylsilyloxy-2-((2Z)-7-(1-ethoxyethoxy)-hepta-2-en-1-yl)-3-((4RS)-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-yne-1-yl) cyclopentanone

[0095]



[0096] To a solution of (1Z)-1-iodo-6-(1-ethoxyethoxy)hexa-1-ene (537 mg) in ether (5 ml) was added dropwise 1.57 M t-butyllithium in pentane solution (2.30 ml) at -78°C. After the mixture was stirred for 1.5 hours, to the mixture was added 0.25 M lithium 2-thienylcyanocuprate in tetrahydrofuran (8.00 ml). After the mixture was stirred for 30 min at same temperature, to the mixture was added dropwise a solution of the compound prepared in reference example 7 (606 mg) in ether (10 ml). The reaction mixture was warmed up to 0 °C for 1 hour. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, extracted with hexane. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane ethyl acetate = 60 : 1 → 30 : 1) to give the title compound (585 mg) having the following physical data.

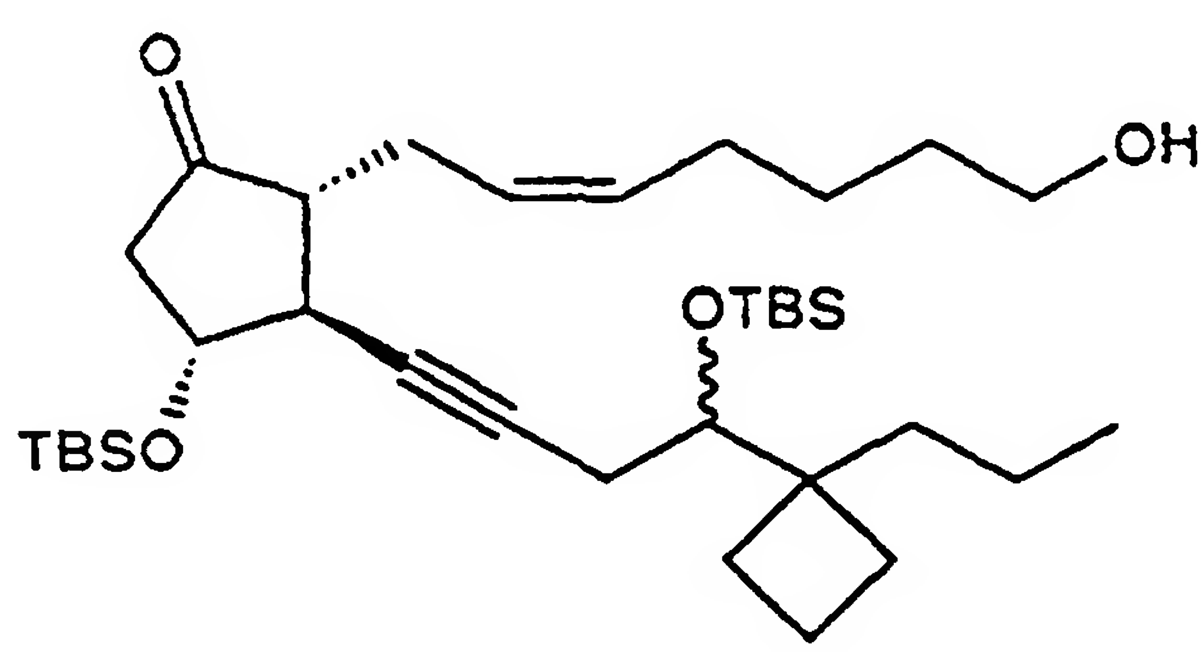
TLC: Rf 0.57 (hexane : ethyl acetate = 6 : 1);

NMR ($CDCl_3$) : δ 5.57-5.28 (2H, m), 465 (1H, q, J=5.0 Hz), 4.32-4.03 (1H, m), 3.73-3.35 (5H, m), 2.74-2.60 (2H, m), 2.47-1.18 (28H, m), 0.96-0.80 (21H, m), 0.13-0.05 (12H, m).

Reference example 9

(5Z,11α,16RS)-11,16-bis(t-butyldimethylsilyloxy)-9-oxo-17,17-propanoprosta-5-ene-13-yne-1-ol

[0097]



[0098] To a solution of the compound prepared in reference example 8 (643 mg) in methanol (14 ml) was added pyridinium p-toluenesulfonate (24 mg) at 0 °C. The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium hydrogencarbonate, extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous

magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give the title compound (399 mg) having the following physical data.

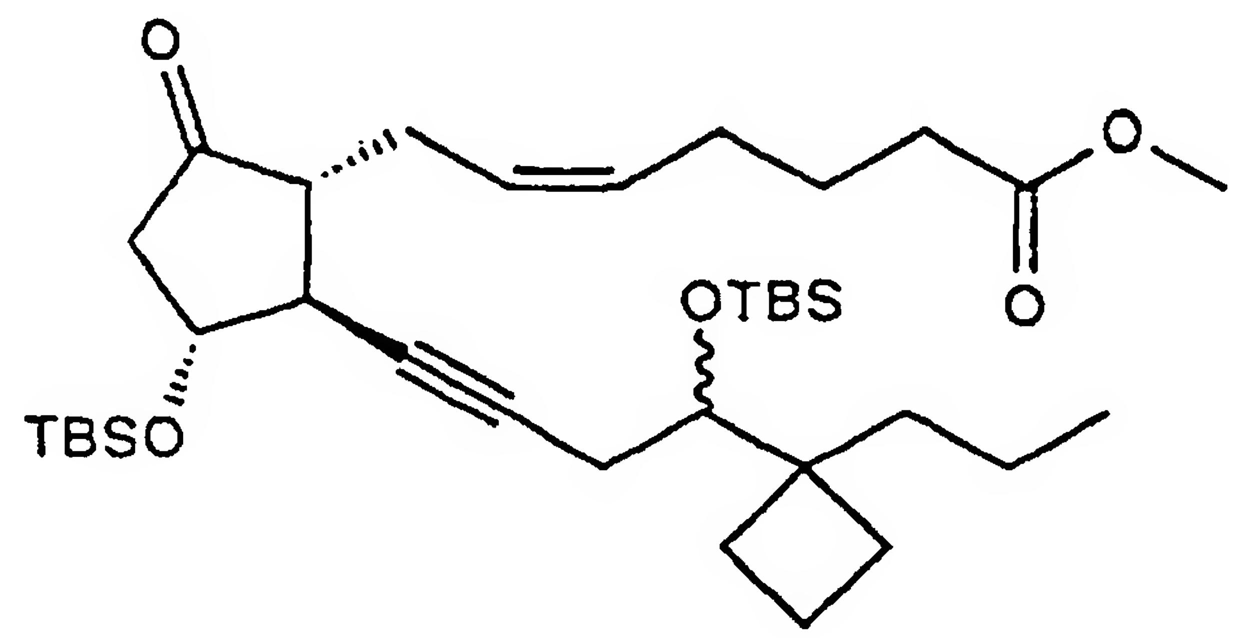
TLC: Rf 0.37 (hexane : ethyl acetate = 4 : 1);

NMR ($CDCl_3$) : δ 5.60-5.30 (2H, m), 4.32-4.22 (1H, m), 3.70 (1H, t, J=6.0 Hz), 3.64 (2H, t, J=7.0 Hz),2.72-2.60 (1H, m), 2.66 (1H, dd, J=17.8, 6.6 Hz), 2.47-1.32 (23H, m), 0.95-0.83 (21H, m), 0.18-0.03 (12H, m).

Reference example 10

(5Z,11α,16RS)-11,16-bis(t-butyldimethylsilyloxy)-9-oxo-17,17-propanoprosta-5-ene-13-ynoio acid · methylester

[0099]



[0100] To a solution of the compound prepared in reference example 9 (369 mg) in acetone (10 ml) was added dropwise Jones reagent (aqueous solution of chromium (VI) oxide and sulfuric acid, 2.0 M containing chromic acid, 1.0 ml) at -30 °C. The reaction mixture was stirred for 1 hour. To the reaction mixture added isopropyl alcohol (3 ml), diluted with water, extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated until the volume of 50 ml. To the residue solution was added a solution of diazomethane in ether until the reaction solution changed yellow color. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 100 : 1) to give the title compound (257 mg) having the following physical data.

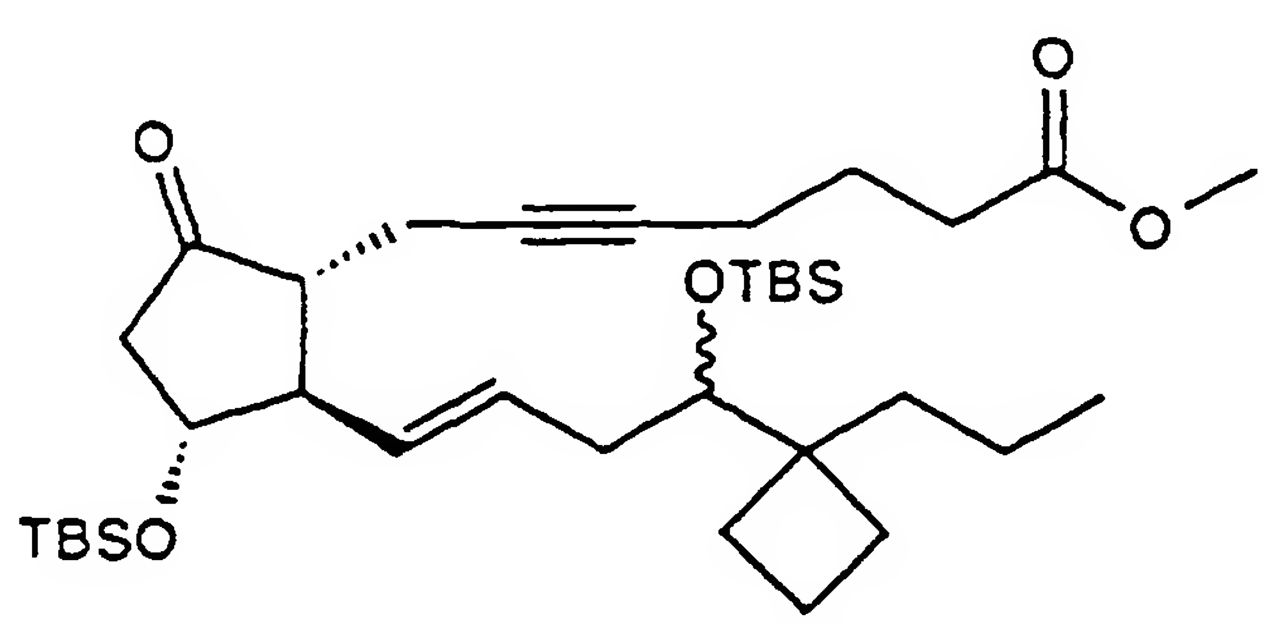
TLC: Rf 0.76 (hexane : ethyl acetate = 4 : 1);

NMR ($CDCl_3$) : δ 5.49-5.35 (2H, m), 4.32-4.22 (1H, m), 3.69 (1H, t, J=4.8 Hz), 3.66 (3H, s), 2.73-2.61 (12H, m), 2.44-1.32 (20H, m), 2.31 (2H, t, J=7.6 Hz), 0.95-0.82 (21 H, m), 0.13-0.06 (12H, m).

Reference example 11

(11α,13E,16RS)-11,16-bis(t-butyldimethylsilyloxy)-9-oxo-17,17-propanoprosta-13-ene-5-ynoic acid · methylester

[0101]



[0102] To a solution of (1E,4RS)-1-iodo-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-ene (265 mg) in ether (2 ml) was added dropwise 1.7 M t-butyllithium in pentane solution (0.83 ml) at -78 °C. After the mixture was stirred for 1 hour, to the mixture was added 0.25 M lithium 2-thienylcyanocuprate in tetrahydrofuran (3.12 ml). After the mixture was stirred for 20 min at same temperature, to the mixture was added dropwise a solution of (4R)-4-t-butyldimethylsilyloxy-2-cyclopenten-1-one (106 mg) in tetrahydrofuran (4 ml). The reaction mixture was warmed up to -20 °C for 30 min. To the reaction mixture was added dropwise a solution of 7-iodohepta-5-ynoic acid · methylester (665 mg) in tetrahydrofuran (5 ml). The reaction mixture was stirred for 3 hours. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, extracted with hexane. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 50 : 1 → 20 : 1) to give the title compound (44 mg) having the following physical data.

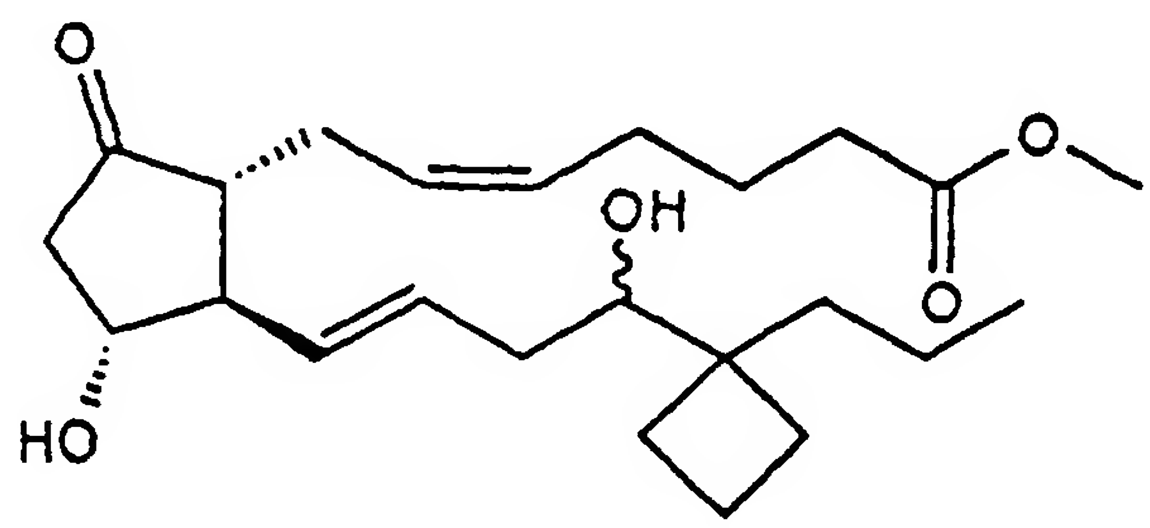
TLC: Rf 0.36(hexane : ethyl acetate = 9 : 1);

NMR ($CDCl_3$) : δ 5.78-5.55 (1H, m), 5.40-5.23 (1H, m), 4.10-3.95 (1H, m), 3.66 (3H, s), 3.63-3.53 (1H, m), 2.80-2.50 (2H, m), 2.50-1.20 (22H, m), 1.00-0.80 (3H, m), 0.91, 0.90 and 0.88 (18H, 3s), 0.09, 0.05 and 0.04 (12H, 3s).

Example 1

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester

[0103]



[0104] To a solution of the compound prepared in reference example 3 (330 mg) in acetonitrile (7 ml) was added pyridine (3 ml) and a 47% aqueous solution of hydrofluoric acid (6 ml). The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture quenched by addition of water, extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane ethyl acetate = 1 : 1) to give the compound of the present invention in the form of each stereoisomer on the 1 6-position, i.e. a less polar compound (55 mg) and a more polar compound (55 mg), having the following physical data.

TLC: Rf 0.37 (hexane ethyl acetate = 2 : 3) ;

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15.3, 7.6, 6.3 Hz), 5.54-5.26 (3H, m), 4.18-4.00 (1H, m), 3.67 (3H, s), 3.55 (1H, dd, J=10.0, 2.4 Hz), 2.75 (1H, ddd, J=18.6, 7.2, 1.0 Hz), 2.85-2.65 (1H, br), 2.50-1.50 (19H, m), 2.32 (2H, t, J=7.5 Hz), 1.50-1.20 (3H, m), 0.94 (3H, t, J=6.9 Hz).

more polar

TLC: Rf 0.29 (hexane : ethyl acetate = 2 : 3);

NMR ($CDCl_3$) : δ 5.69 (1H, ddd, J=15.4, 8.2, 5.4 Hz), 5.49-5.25 (3H, m), 4.12-3.98 (1H, m), 3.67 (3H, s) 3.65-3.20 (1H, br), 3.55 (1H, dd, J=10.2, 2.4 Hz), 2.74 (1H, ddd, J=18.4, 7 4, 1.0 Hz), 2.50-1.50 (19H, m), 2.31 (2H, t, J=7.3 Hz). 1.50-1.20 (3H, m), 0.94 (3H, t, J=6.9 Hz).

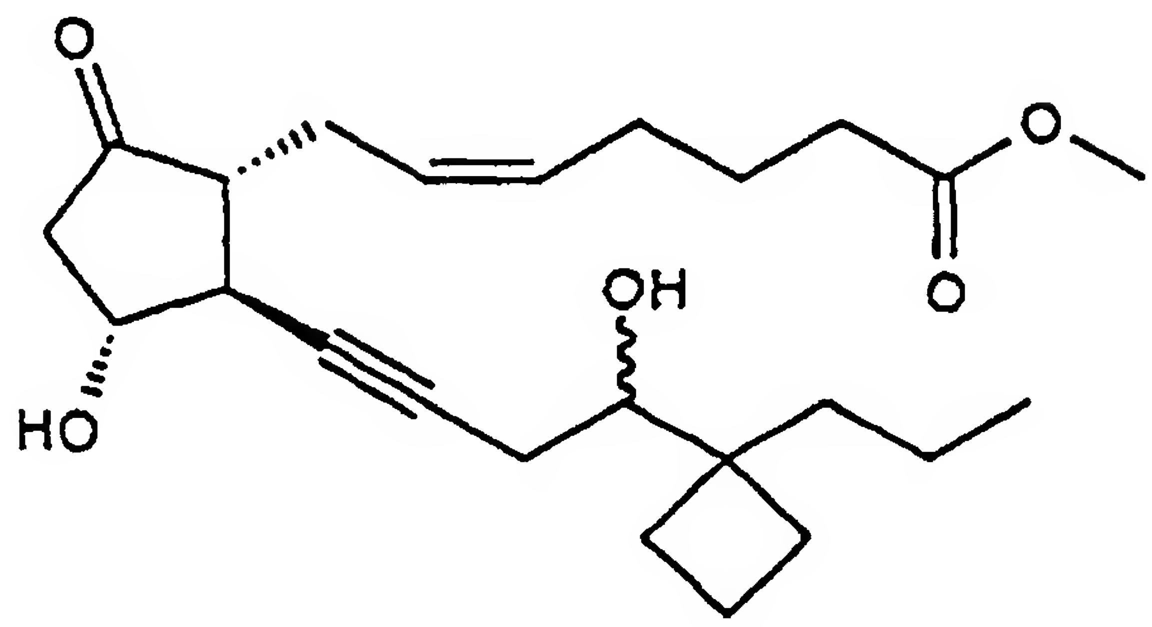
Example 1(1)~1(2)

[0105] By the same procedure as provided in example 1, using the compound prepared in reference example 10 or reference example 11, compounds of the present invention having the following physical data were obtained.

Example 1(1)

(5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-ene-13-ynoic acid · methylester

[0106]



mixture

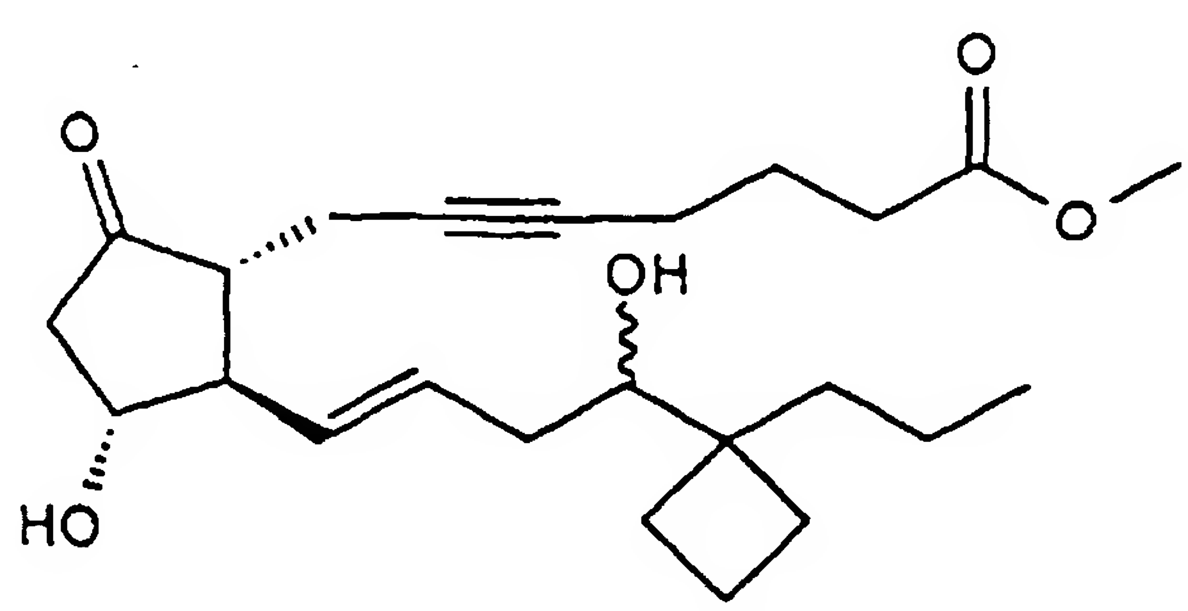
TLC: Rf 0.57 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.54-5.31 (2H, m), 4.39-4.27 (1H, m), 3.70-3.63 (1H, m), 3.67 (3H, s), 3.40-3.30 (1H, brs), 2.75 (1H, dd, J=18.4, 7.2 Hz), 2.72-1.20 (24H, m), 0.93 (3H, t, J=7.0 Hz).

Example 1(2)

(11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-13-ene-5-ynoic acid · methylester

[0107]



less polar

TLC: Rf 0.33 (hexane ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.80 (1H, ddd, J=15.4, 7.6, 6.2 Hz), 5.52 (1H, dd, J=15.4, 8.2 Hz), 4.22-4.06 (1H, m), 3.68 (3H, s), 3.59 (1H, dd, J=9.8, 2.8 Hz), 2.90-2.55 (3H, m), 2.50-1.20 (21H, m), 2.43 (2H, t, J=7.6 Hz), 0.94 (3H, t, J=6.8 Hz).

more polar

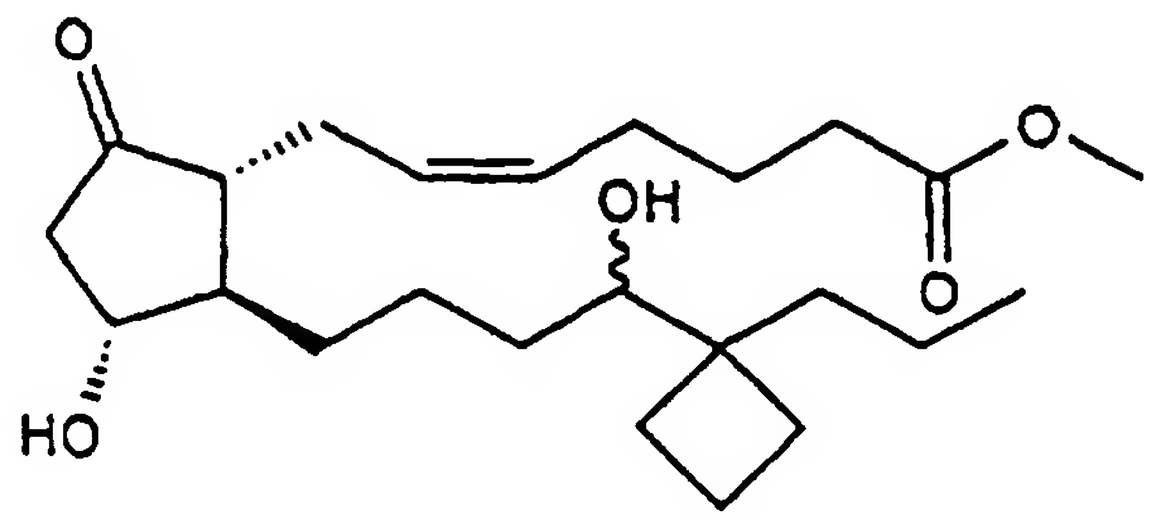
TLC: Rf 0.24 (hexane ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.76 (1H, ddd, J=15.4, 8.2, 5.4 Hz), 5.46 (1H, dd, J=15.4, 8.6 Hz), 4.19-4.03 (1H, m), 3.68 (3H, s), 3.58 (1H, dd, J=10.0, 2.2 Hz), 2.90-2.55 (3H, m), 2.50-1.20 (21H, m), 2.43 (2H, t, J=7.4 Hz), 0.94 (3H, t, J=6.8 Hz).

Example 2

(5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-enoic acid · methylester

[0108]



[0109] By the same procedure as provided in reference example 3 → example 1, using the compound prepared in reference example 6, compound of the present invention having the following physical data was obtained.
mixture
TLC: Rf 0.34 (hexane : ethyl acetate = 1 : 2);
NMR ($CDCl_3$) : δ 5.51-5.28 (2H, m), 4.28-4.16 (1H, m), 3.67 (3H, s), 3.55-3.50 (1H, m), 2.68 (1H, odd, J=19, 7, 3 Hz), 2.50-1.20 (25H, m), 2.33 (2H, t, J=7 Hz), 0.93 (3H, t, J=7 Hz).

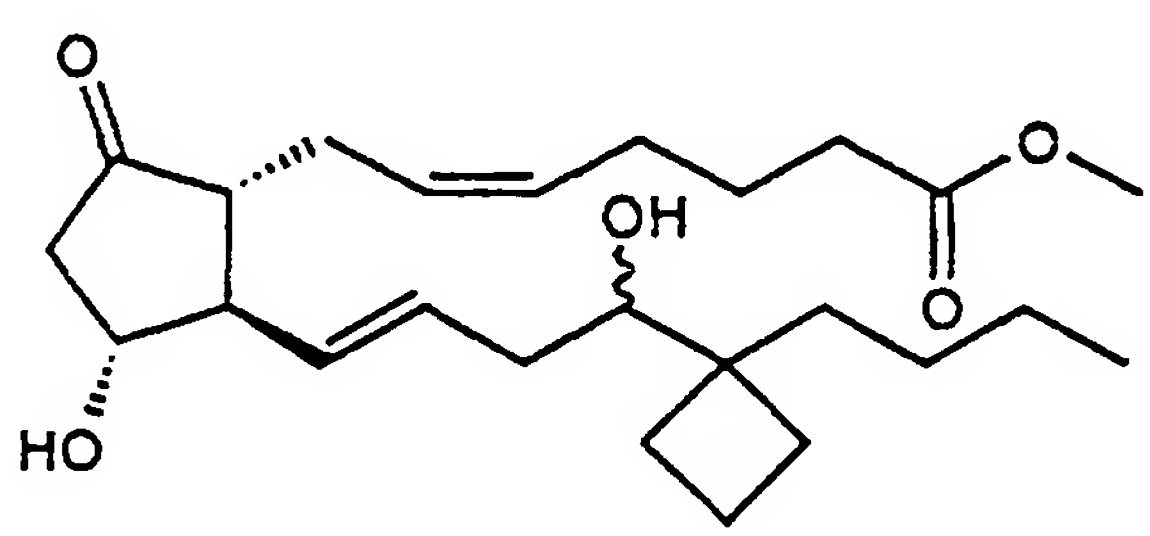
Example 3~3(9)

[0110] By the same procedure as provided in reference example 1 → reference example 2 → reference example 3 → example 1, using corresponding acetylene derivatives instead of (4RS)-5,5-propanoocta-1-yne-4-ol as starting material in reference example 1, compounds of the present invention having the following physical data were obtained.

Example 3

(5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester

[0111]

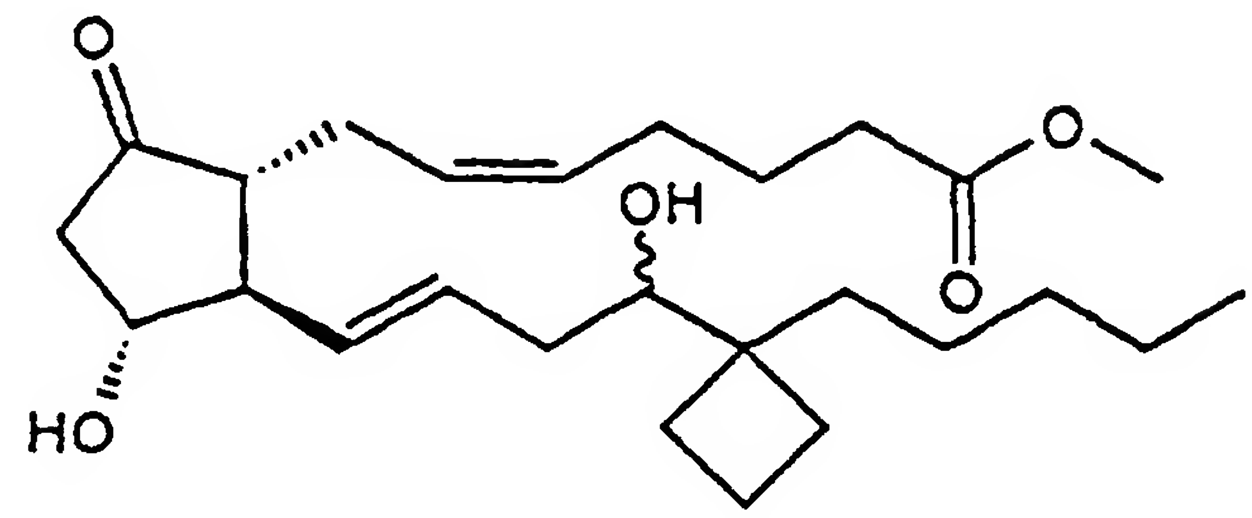


less polar
TLC: Rf 0.32 (hexane : ethyl acetate = 1 : 1);
NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15, 8, 6 Hz), 5.52-5.27 (3H, m), 4.17-4.03 (1H, m), 3.67 (3H, s), 3.54 (1H, dd, J=10, Hz), 2.75 (1H, dd, J=19, 8 Hz), 2.50-1.90 (9H, m), 2.30 (2H, t, J=7 Hz), 1.90-1.20 (14H, m), 0.90 (3H, t, J=7 Hz).
more polar
TLC: Rf 0.28 (hexane : ethyl acetate = 1 : 1);
NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J = 15, 8, 6 Hz), 5 50-5.27 (3H, m), 4.17-4.00 (1H, m), 3.66 (3H, s), 3.56 (1H, dd, J=10, 2 Hz), 2.74 (1H, dd, J=17, 6 Hz), 2.48-1.20 (23H, m), 2.30 (2H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz).

Example 3(1)

(5Z,11α,13E)-11,16-dihydroxy-20-ethyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester

[0112]



less polar

TLC: Rf 0.31 (hexane : ethyl acetate = 1 : 1);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15, 8, 6 Hz), 5.52-5.27 (3H, m), 4.15-4.02 (1H, m), 3.67 (3H, s), 3.54 (1H, dd, J=10, 2 Hz); 2.75 (1H, dd, J=19, 8 Hz), 2.50-1.90 (9H, m), 2.32 (2H, t, J=7 Hz), 1.90-1.20 (16H, m), 0.90 (3H, t, J=7 Hz).

more polar

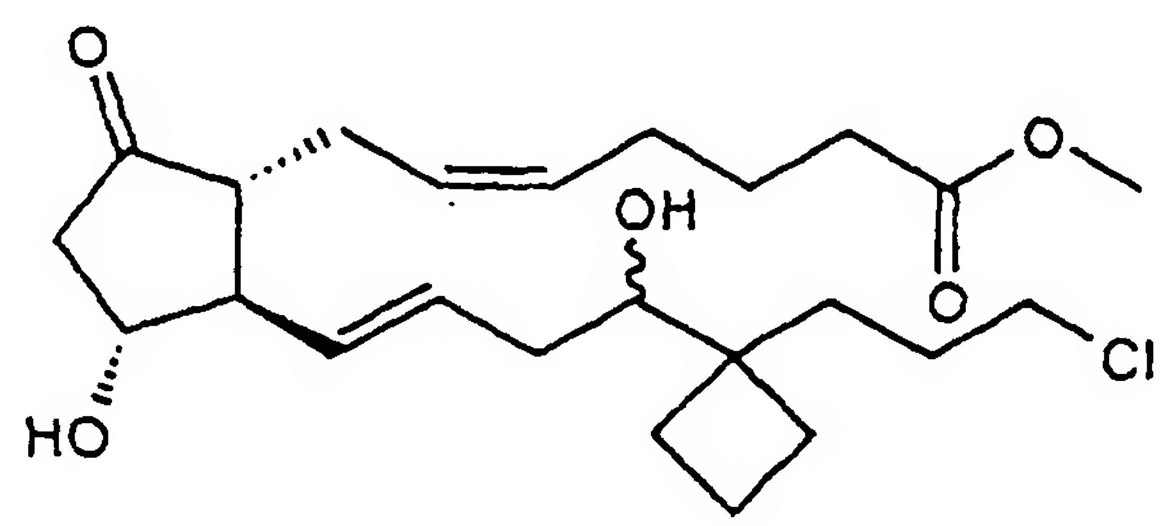
TLC: Rf 0.27 (hexane : ethyl acetate =1 : 1);

NMR ($CDCl_3$) : δ 5.72 (1H, ddd, J=15, 8, 6 Hz), 5.49-5.27 (3H, m), 4.12-3.99 (1H, m), 3.66 (3H, s), 3.55 (1H, dd, J=10, 2 Hz), 2.75 (1H, dd, J=19, 8 Hz), 2.50-1.90 (9H, m), 2.33 (2H, t, J=7 Hz), 1.90-1.10 (16H, m), 0.90 (3H, t, J=7 Hz).

Example 3(2)

(5Z,11α,13E)-20-chloro-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester

[0113]



less polar

TLC: Rf 0.24 (hexane : ethyl acetate = 1 : 2);

NMR($CDCl_3$) : δ 5.70 (1H, ddd, J=15, 8, 6 Hz), 5.53-5.26 (3H, m), 4.17-4.03 (1H, m), 3.67 (3H, s), 3.59-3.53 (3H, m), 2.76 (1H, dd, J=18, 8 Hz), 2.50-1.45 (21H, m), 2.30 (2H, t, J=7 Hz).

more polar

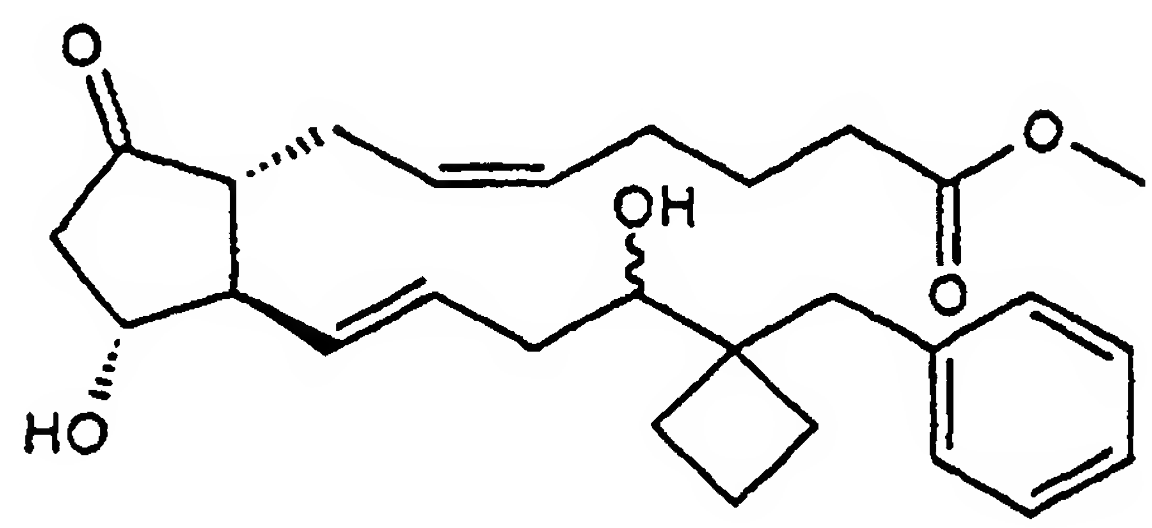
TLC: Rf 0.18 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$): δ 5.70 (1H, ddd, J=15, 8, 6 Hz), 5.50-5.26 (3H, m), 4.17-4.00 (1H, m), 3.66 (3H, s), 3.59-3.53 (3H, m), 2.74 (1H, dd, J=19, 7 Hz), 2.50-1.50 (21H, m), 2.30 (2H, t, J=7 Hz).

Example 3(3)

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-18-phenyl-17,17-propano-19,20-dinorprosta-5,13-dienoic acid · methylester

[0114]



less polar

TLC: Rf 0.29 (hexane : ethyl acetate = 1 : 2);

NMR($CDCl_3$) δ 7.33-7.20 (5H, m), 5.70 (1H, ddd, J=15. 8,6 Hz), 5.54-5.27 (3H, m), 4.18-4.03 (1H, m), 3.66 (3H, s), 3.57 (1H, dd, J=10, 2 Hz), 2.92 (1H, d, J=13 Hz), 2.76 (1H, dd, J=1 9, 7 Hz), 2.65 (1H, d, J=13 Hz), 2.50-1.45 (17H, m), 2.30 (2H, t, J=7 Hz).

more polar

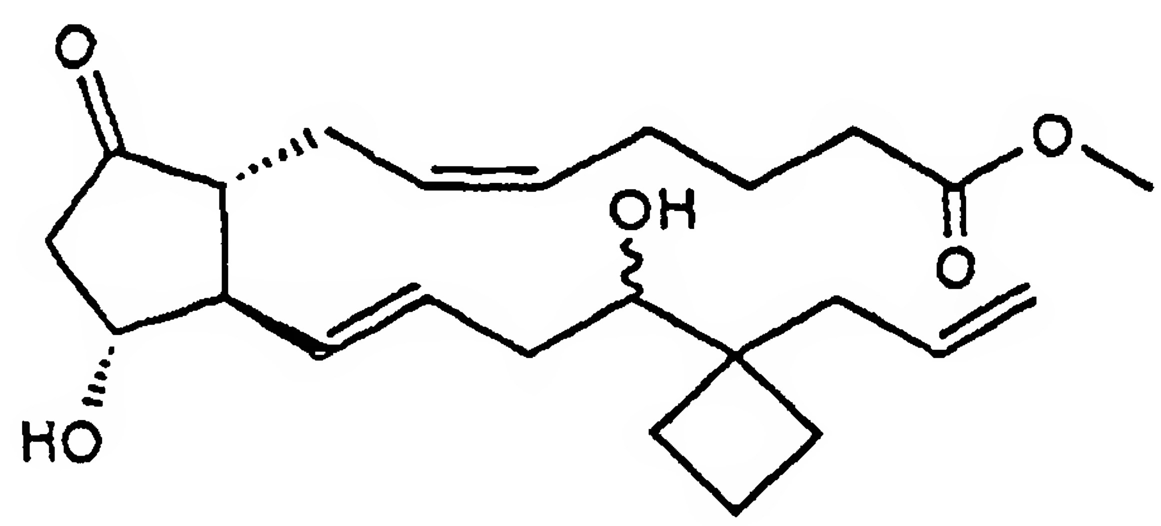
TLC: Rf 0.21 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 7.36-7.18 (5H, m), 5.70 (1H, ddd, J= 15, 8, 6 Hz), 5.49-5.26 (3H, m), 4.18-3.99 (1H, m), 3.65 (3H, s), 3.57 (1H, dd, J=10, 2 Hz), 2.91 (1H, d, J=14 Hz), 2.73 (1H, dd, J=1 8, 7 Hz), 2.66 (1H, d, J=14 Hz), 2.50-1.45 (17H, m), 2.30 (2H, t, J=7 Hz).

Example 3(4)

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13,19-trienoic acid · methylester

[0115]



less polar

TLC: Rf 0.44 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.95 (1H, ddt, J=17.0, 10.0, 7.4 Hz), 5.71 (1H, ddd, J=15.4, 7.7, 5.9 Hz), 5.60-5.25 (3H, m), 5.20-5.05 (2H, m), 4.16-4.02 (1H, m), 3.67 (3H, s), 3.56 (1H, dd, J=9.6, 2.0 Hz), 2.76 (1H, ddd, J=18.3, 7.3, 1.4 Hz), 2.50-1.55 (21H, m), 2.32 (2H, t, J=7.5 Hz).

more polar

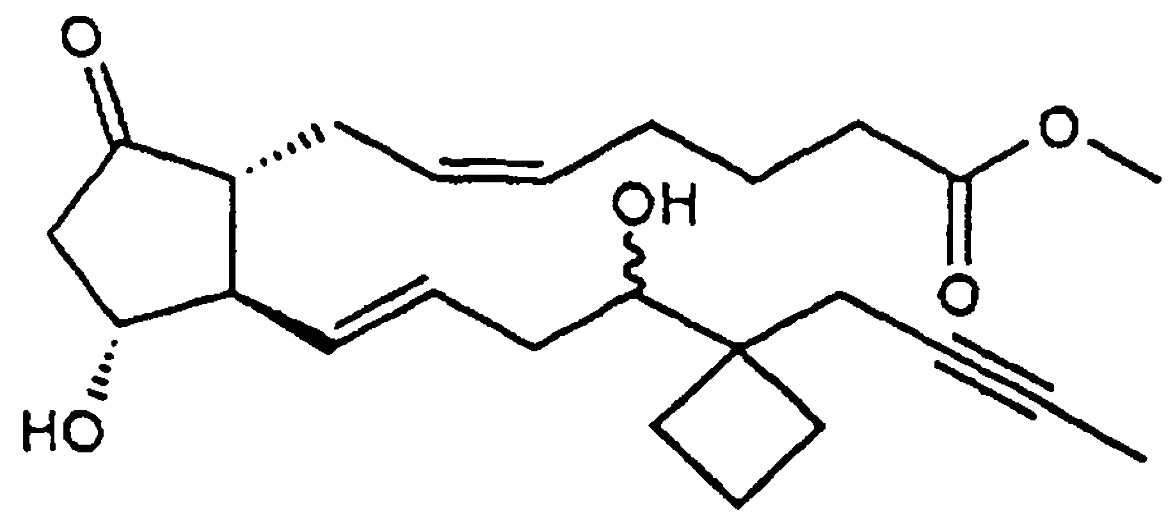
TLC: Rf 0.34 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.95 (1H, ddt, J=17.2, 10.0, 7.4 Hz), 5.70 (1H, ddd, J=15.4, 7.6, 5.6 Hz), 5.57-5.25 (3H, m), 5.20-5.05 (2H, m), 4.14-3.98 (1H, m), 3.67 (3H, s), 3.56 (1H, dd, J=10.2, 2.3 Hz), 3.00-2.70 (1H, br), 274 (1H, ddd, J=18.2, 7.4, 14 Hz), 2.50-1.55 (20H, m), 2.32 (2H, t, J=7.5 Hz).

Example 3(5)

(5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-diene-19-ynoic acid · methylester

[0116]



less polar

TLC: Rf 0.43 (hexane : ethyl acetate = 1:2);

NMR ($CDCl_3$) : δ 5.83-5.66 (1H, m), 5.55-5.25 (3H, m), 4.18-4.00 (1H, m), 3.75-3,60 (1H, m), 3.67 (3H, s), 2.75 (1H, ddd, J=18.4, 7.4, 1.4 Hz), 2.50-1.55 (21H, m), 2.32 (2H, t, J=7.4 Hz), 1.80 (3H, t, J=2.6 Hz).

more polar

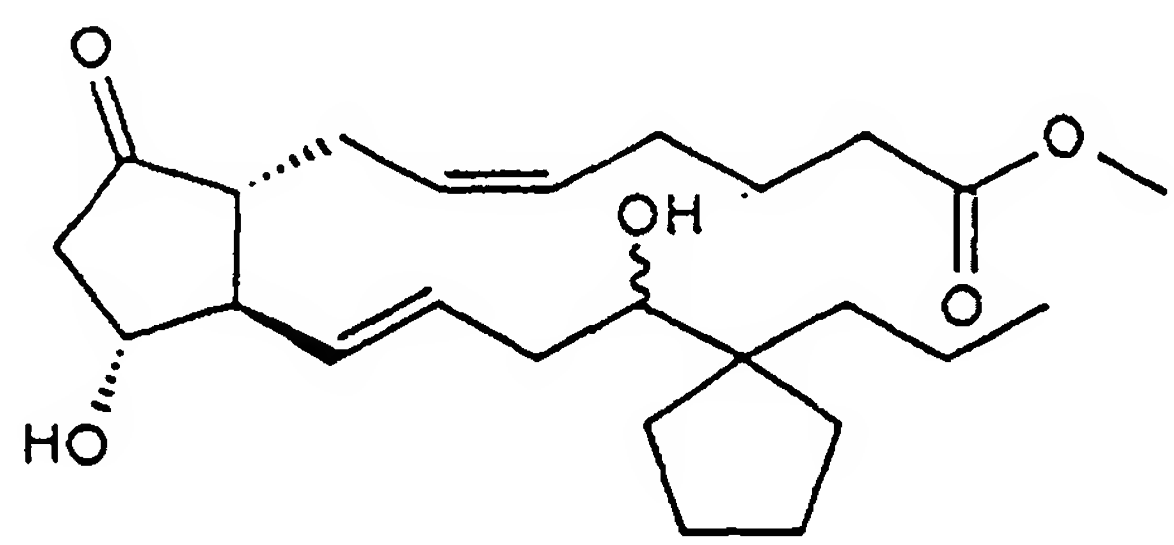
TLC: Rf 0.33 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.72 (1 H, ddd, J=15.0, 7.8, 5.8 Hz), 5.52-5.25 (3H, m), 4.15-3.98 (1H, m), 3.73-3.62 (1H, m), 3.67 (3H, s), 2.74 (1H, ddd, J=18.4, 7.2, 1.4 Hz), 2.50-1.50 (21 H, m), 2.32 (2H, t, J=7.2 Hz), 1.80 (3H, t, J=2.6 Hz).

Example 3(6)

(5Z,11α,13E)-17,17-butano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester

[0117]



less polar

TLC: Rf 0.43 (hexane : ethyl acetate = 2 : 3);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15.2, 7.9, 5.7 Hz), 5.54-5.25 (3H, m), 4.14-4.01 (1H, m), 3.67 (3H, s), 3.47 (1H, dd, J=10.2, 2.0 Hz), 2.75 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.80 (10H, m), 2.32 (2H, t, J=7.4 Hz), 1.80-1.50 (9H, m), 1.50-1.20 (6H, m), 0.90 (3H, t, J=6.8 Hz).

more polar

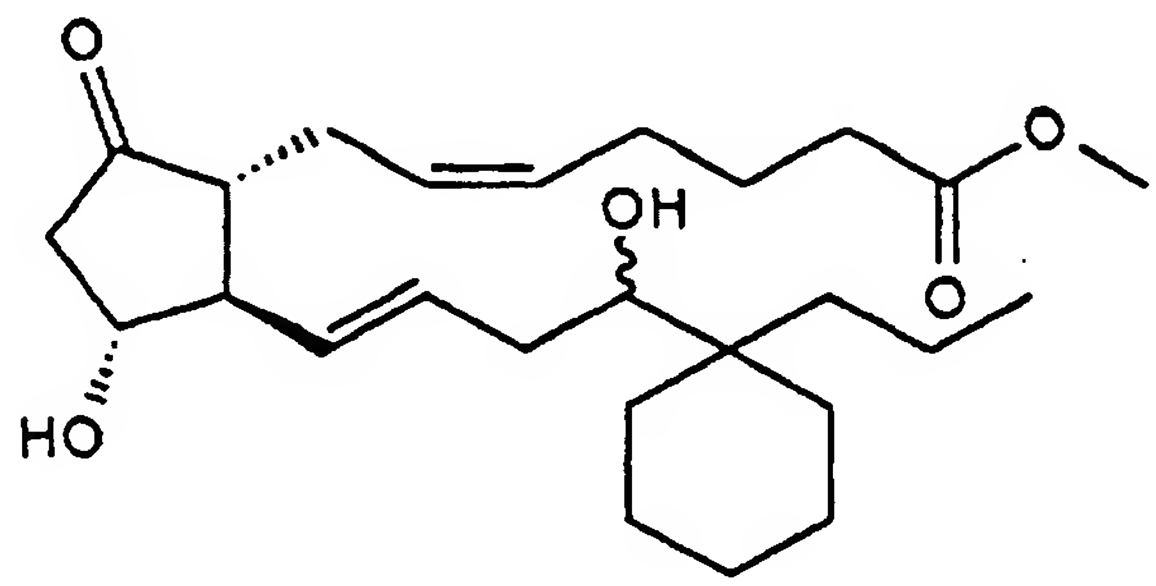
TLC: Rf 0.34 (hexane : ethyl acetate = 2 : 3);

NMR ($CDCl_3$) : δ 5.67 (1H, ddd, J=15.2, 8.2, 5.2 Hz), 5.48-5.25 (3H, m), 4.12-3.96 (1H, m), 3.70-3.40 (1H, br), 3.67 (3H, s), 3.48 (1H, dd, J=10.2, 2.0 Hz), 2.75 (1H, ddd, J=18.4, 7.6, 1.0 Hz), 2.50-1.80 (10H, m), 2.31 (2H, t, J=7.5 Hz), 1.80-1.50 (8H, m), 1.50-1.20 (6H, m), 0.90 (3H, t, J=6.6 Hz).

Example 3(7)

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-pentanoprosta-5,13-dienoic acid · methylester

[0118]



less polar

TLC: Rf 0.47 (hexane : ethyl acetate = 2 : 3);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15.4, 8.0. 5.6 Hz), 5.53-5.25 (3H, m), 4.16-4.01 (1H, m), 367 (3H, s) 3.47 (1H, dd, J=10.6, 2.0 Hz), 2.75 (1H, ddd, J=18.6, 7.4, 1.2 Hz), 2.50-2.00 (10H, m), 2.32 (2H, t, J=7.4 Hz), 2.00-1.15 (17H, m), 0.91 (3H, t, J=6.5 Hz).

more polar

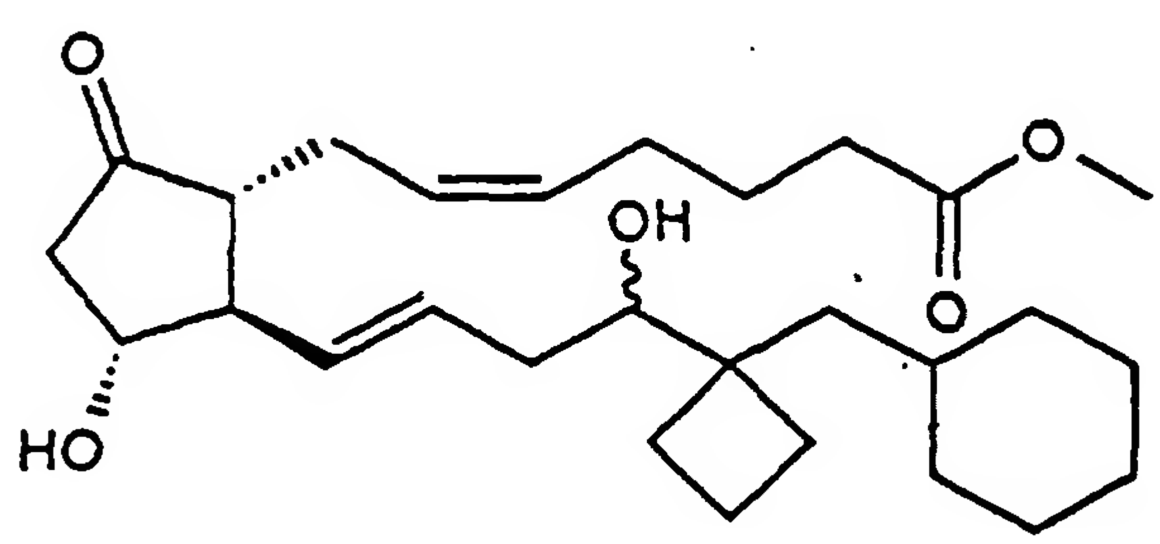
TLC: Rf 0.38 (hexane : ethyl acetate = 2 : 3);

NMR ($CDCl_3$) : δ 5.69 (1 H, ddd, J=15.4, 8.0, 5.6 Hz), 5.48-5.25 (3H, m), 4.12-3.96 (1H, m), 3.67 (3H, s), 3.60-3.00 (1H, br), 3.47 (1H, dd, J=10.5, 1.7 Hz), 2.73 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.95 (10H, m), 2.31 (2H, t, J=7.4 Hz), 1.80-1.15 (16H, m), 0.91 (3H, t, J=6.7 Hz).

Example 3(8)

(5Z,11α,13E)-18-cyclohexyl-11,16-dihydroxy-9-oxo-17,17-propano-19,20-dinorprosta-5,13-diencic acid · methylester

[0119]



less polar

TLC: Rf 0.40 (hexane : ethyl acetate = 2 : 3);

NMR ($CDCl_3$) : δ 5.74 (1H, ddd, J=15.2, 8.0, 6.0 Hz), 5.60-5.25 (3H, m), 4.18-4.02 (1H, m), 3.67 (3H, s), 3.67-3.56 (1H, m), 2.76 (1H, dd, J=18.2, 7.8 Hz), 2.60-1.95 (13H, m), 2.33 (2H, t, J=7.6 Hz), 1.95-1.45 (12H, m), 1.45-0.85 (7H, m).

more polar

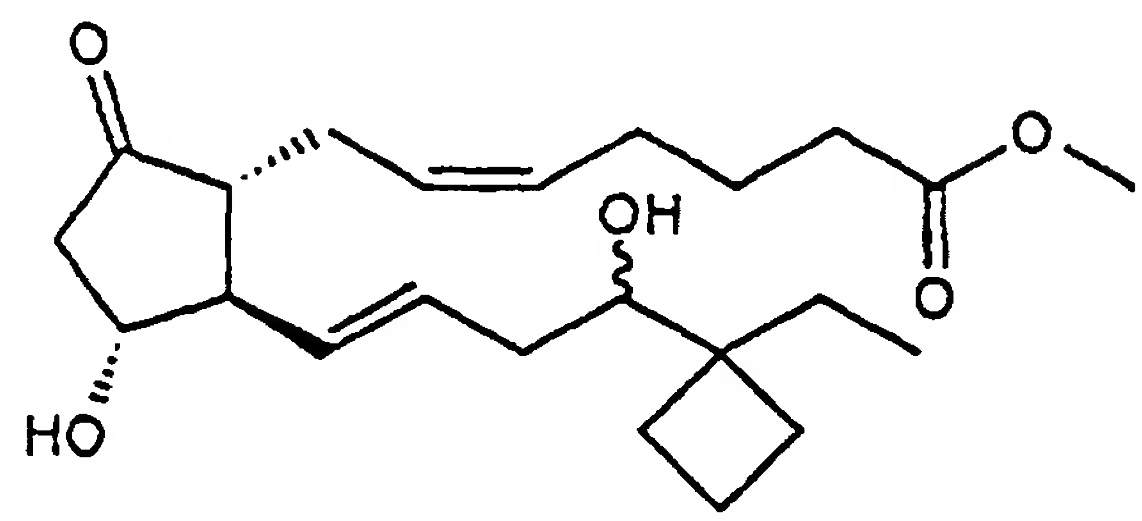
TLC: Rf 0.35 (hexane : ethyl acetate = 2 : 3);

NMR ($CDCl_3$) : δ 572 (1H, ddd, J=15.4, 8.2, 5.2 Hz), 5.50-5.25 (3H, m), 4.14-3.98 (1H, m), 3.67 (3H, s), 3.61 (1H, dd, J=10.2, 2.0 Hz), 3.49 (1H, br), 2.74 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.60-1.95 (12H, m), 2.32 (2H, J=7.6 Hz), 1.95-1.45 (12H, m), 1.45- 0.85 (7H, m).

Example 3(9)

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-dienoic acid · methylester

[0120]



less polar

TLC: Rf 0.35 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15, 8, 6 Hz), 5.52-5.24 (3H, m), 4.15-4.03 (1H, m), 3.67 (3H, s), 3.56 (1H, dd, J= 10,2 Hz), 2.75 (1H, ddd, J=19, 7, 1 Hz), 2.50-1.35 (19H, m), 2.34 (2H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz).

more polar

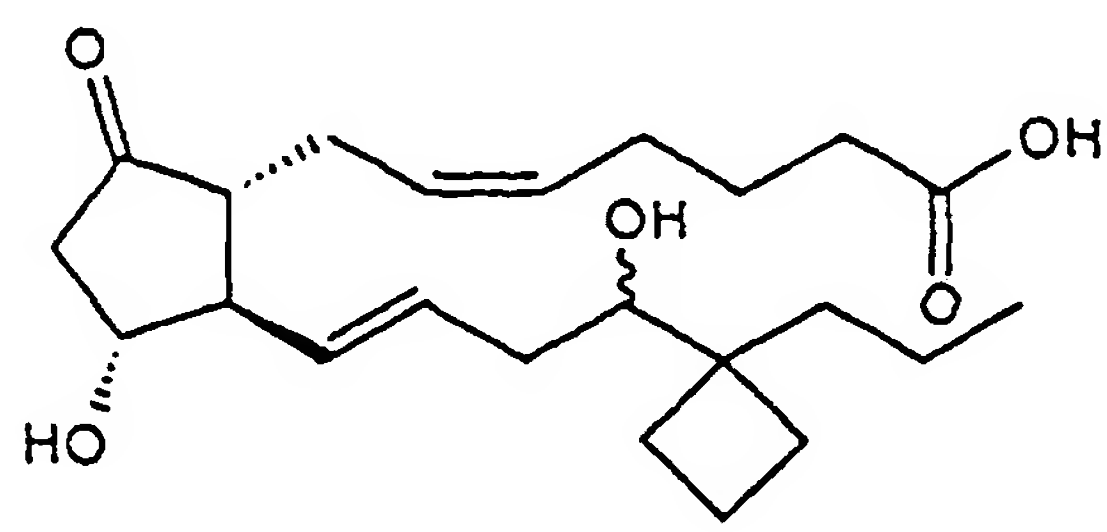
TLC: Rf 0.26 (hexane : ethyl acetate = 1 2);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15, 8, 6 Hz), 5.48-5.26 (3H, m), 4.12-3.99 (1H, m), 3.66 (3H, s), 3.56 (1H, dd, J= 10, 2 Hz), 2.73 (1H, ddd, J=19, 7, 1 Hz), 2.48-1.47 (19H, m), 2.34 (2H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz).

Example 4

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-dienoic acid

[0121]



[0122] To the mixture of the less polar compound prepared in example 1 (55 mg) in ethanol (0.4 ml) and phosphate buffer (pH 7.4, 4 ml) was added PLE (pig liver esterase, 20 μl) at room temperature. The reaction mixture was stirred for 3 hours. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium sulfate, extracted with ethyl acetate. The extract was washed with 1 N aqueous solution of hydrochloric acid and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1 → ethyl acetate) to give the present invention compound (33 mg) having the following physical data. By the same procedure as provided in the above method, using the more polar compound prepared in example 1, compound (29 mg) of the present invention having the following physical data were obtained.

less polar

TLC: Rf 0.41 (ethyl acetate : hexane : acetic acid = 16 : 8 : 1);

NMR ($CDCl_3$) : δ 5.74 (1H, dt, J=15.0, 6.0 Hz), 5.55-5.25 (3H, m), 4.08 (1 H, q, J=7.5 Hz), 3.64 (1H, do, J=10.5,

2.5 Hz), 2.75 (1H, dd, J=18.0, 7.5 Hz), 2.50-2.20 (7H, m), 2.20-1.20 (18H, m), 0.94 (3H, t, J=7.0 Hz).
more polar

TLC: Rf 0.36 (ethyl acetate : hexane : acetic acid = 16 : 8 : 1);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=14.0, 8.0, 6.0 Hz), 5.54-5.30 (3H, m), 4.05 (1H, q, J=8.5 Hz), 3.61 (1H, dd, J=10.0, 2.5 Hz), 2.74 (1H, dd, J=19.0, 8.0 Hz), 2.50-2.20 (7H, m), 2.20-1.20 (18H, m), 0.95 (3H, t, J=6.5 Hz).

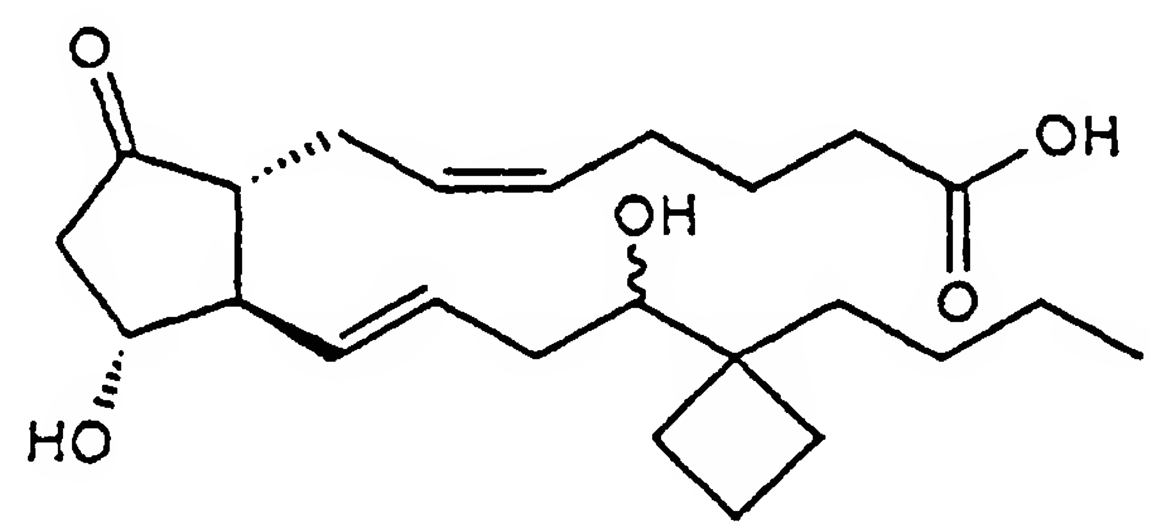
Example 4(1)~4(13)

[0123] By the same procedure as provided in example 4, using the compound prepared in example 3-3(9), example 2 or example 1(1)-1(2), compounds of the present invention having the following physical data were obtained.

Example 4(1)

(5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid

[0124]



less polar

TLC: Rf 0.74 (ethyl acetate : acetic acid = 50 : 1);

NMR($CDCl_3$) : δ 5.72 (1H, dt, J=16, 7 Hz), 5.52-5.31 (3H, m), 5.10-4.50 (3H, brs), 4.14-4.01 (1H, m), 3.60 (1H, dd, J=16, 2 Hz), 2.74 (1H, dd, J=18, 7 Hz), 2.45-1.15 (25H, m), 0,90 (3H, t, J=7 Hz).

more polar

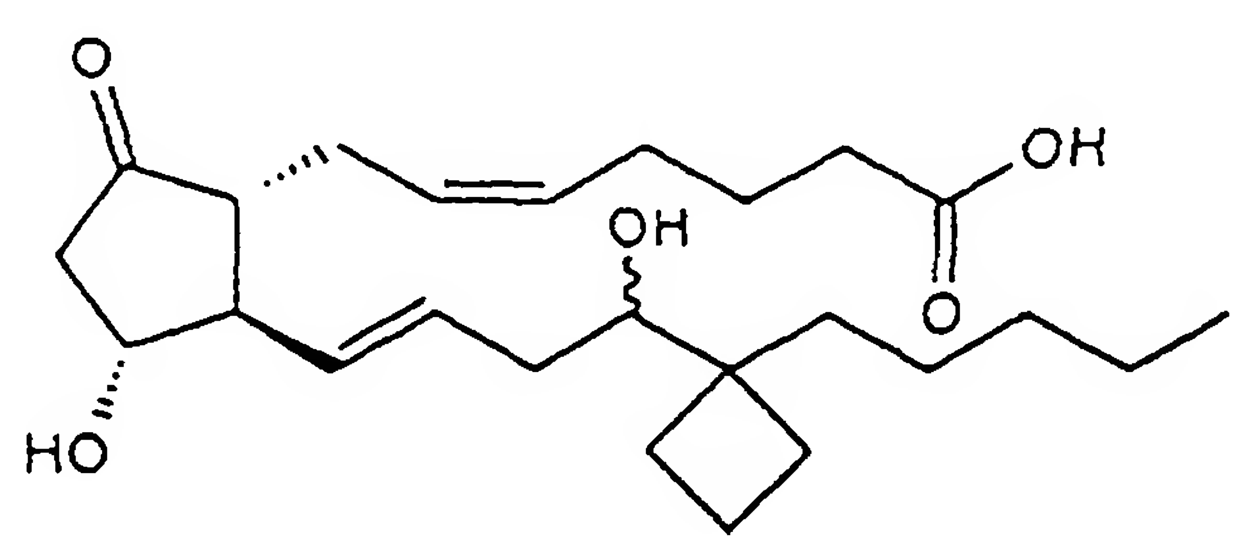
TLC: Rf 0.67 (ethyl acetate : acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 5.90-4.80 (7H, m), 4.10-3.98 (1H, m), 3.56 (1H, d, J=9 Hz), 2.72 (1H, dd, J=18, 7 Hz), 2.47-1.15 (23H, m), 2.30 (2H, t, J=7 Hz), 0.90 (3H, t, J=7 Hz).

Example 4(2)

(5Z,11α,13E)-11,16-dihydroxy-20-ethyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid

[0125]



less polar

TLC: Rf 0.80 (ethyl acetate : acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 5.72 (1H dt, J=15, 7 Hz), 5.52-5.31 (3H,m), 5.60-4.40 (3H, brs), 4.14-4.01 (1H, m), 3.50 (1H, dd, J=11, 2 Hz), 2.74 (1H, dd, J=18, 8 Hz), 2.45- 1.18 (25H, m), 2.34 (2H, t, J=7 Hz), 0.90 (3H, t, J=7 Hz).

more polar

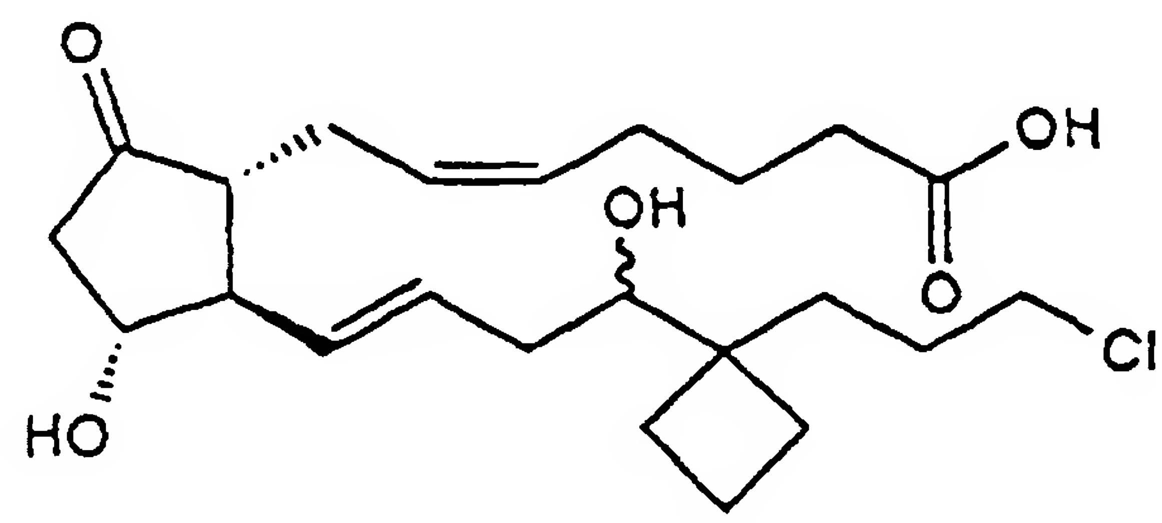
TLC: Rf 0.73 (ethyl acetate : acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 5.76-5.61 (1H, m), 5.49-5.32 (3H, m), 4.80-4.20 (3H, brs), 4.11-3.98 (1H, m), 3.59 (1H, dd, J=10, 1 Hz), 2.73 (1H, dd, J=18, Hz), 2.45-1.15 (25H, m), 2.35 (2H, t, J=7 Hz), 0.90 (3H, t, J=7 Hz).

Example 4(3)

(5Z,11α,13E)-20-chloro-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-dienoic acid

[0126]



less polar

TLC: Rf 0.50 (ethyl acetate : acetic acid, 50:1)

NMR ($CDCl_3$) : δ 5.80-5.65 (1H, m), 5.54-5.38 (3H, m), 4.20-3.00 (3H, br), 4.17-4.02 (1H, m). 3.63 (1H, dd, J=10, 2 Hz), 3.56 (2H, t, J=6.2 Hz), 2.76 (1H, dd, J=17.8, 6.8 Hz), 2.46-1.48 (2.3H, m).

more polar

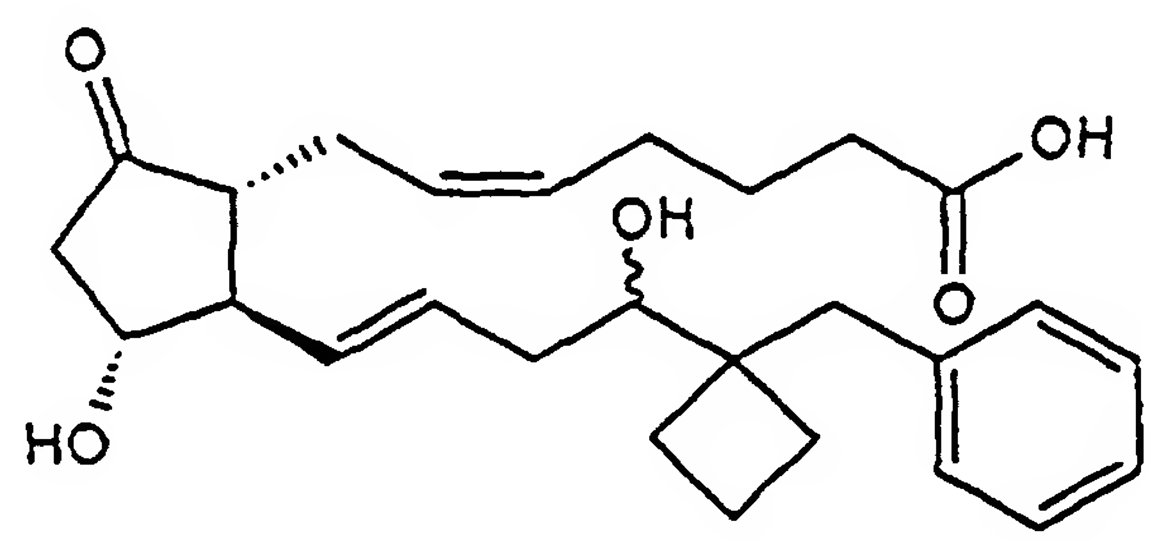
TLC: Rf 0.44 (ethyl acetate · acetic acid = 50 : 1),

NMR ($CDCl_3$) : δ 5.68 (1H, ddd, J=15, 7,5 Hz), 5.50-5.29 (3H, m), 4.80-4.00 (3H, br), 4.12-3.99 (1H, m), 3.63-3.53 (3H, m), 2.74 (1H, dd, J=18,7 Hz), 2.45-1.50 (21H, m), 2.30 (2H, t, J =7 Hz).

Example 4(4)

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-16-phenyl-17,17-propano-19,20-dinorprosta-5,13-dienoic acid

[0127]



less polar

TLC: Rf 0.52 (ethyl acetate : acetic acid = 50 : 1);

NMR($CDCl_3$) : δ 7.37-7.18 (5H, m), 5.72 (1H, ddd, J=15, 7, 6 Hz), 5.54-5.40 (3H, m), 4.14-4.01 (1H, m), 3.67 (1H, dd, J=10, 2 Hz), 3.50-2.90 (3H, brs), 2.90 (1H, d, J=14 Hz), 2.75 (1H, dd, J=19, 8 Hz), 2.66 (1H, d, J=14 Hz), 2.47-1.45 (17H, m), 2.31 (2H, t, J=7 Hz).

more polar

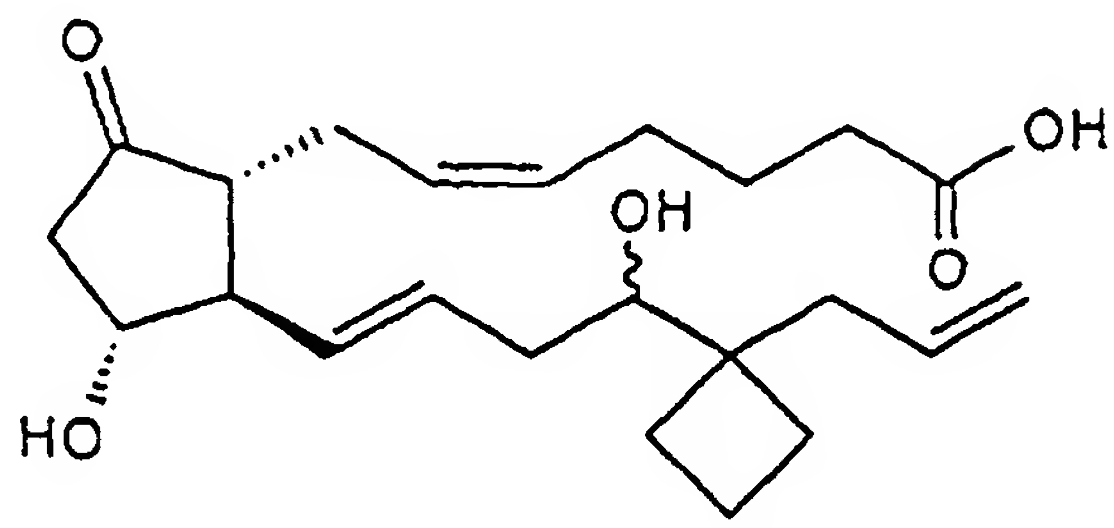
TLC: Rf 0.43 (ethyl acetate acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 7.37-7.18 (5H, m), 5.67 (1 H, ddd, J=15, 8, 6 Hz), 5.49-5.28 (3H, m), 5.20-4.60 (3H, brs), 4.18-3.98 (1H, m), 3.62 (1H, brd, J=10 Hz), 2.87 (1H, d, J=14 Hz), 2.73 (1H, dd, J=18, 8 Hz), 2.65 (1H, d, J=14 Hz), 2.45-1.42 (19H, m).

Example 4(5)

(5Z,11α,13E-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-19-trienoic acid

[0128]



less polar

TLC: Rf 0.28 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.94 (1H, ddt, J=17.0, 10.0, 7.4 Hz), 5.72 (1H, ddd, J=15.0, 7.8, 6.2 Hz), 5.60-5.30 (3H, m), 5.20-5.05 (2H, m), 5.00-4.00 (3H, br), 4.16-4.00 (1H, m), 3.63 (1H, dd, J=10.2, 2.4 Hz), 2.75 (1H, ddd, J=18.2, 7.4, 1.0 Hz), 2.50-1.60 (21H, m).

more polar

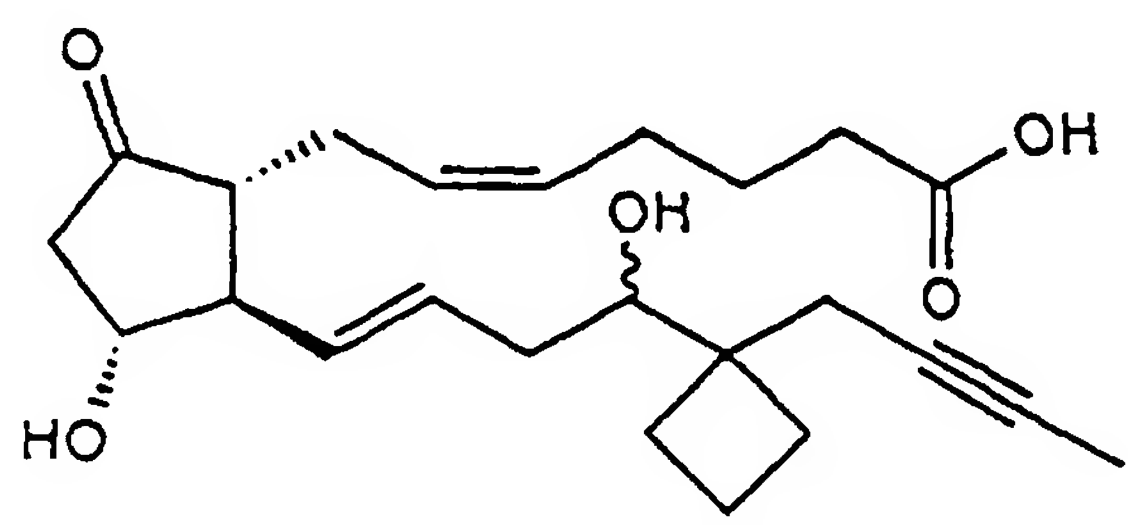
TLC: Rf 0.21 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.94 (1H, ddt. J=17.2, 10.2, 7.2 Hz), 5.66 (1H, ddd, J=15.2, 8.0, 5.6 Hz), 5.53-5.25 (3H, m), 5.30-4.50 (3H, br), 5.20-5.00 (2H, m), 4.12-3.96 (1H, m), 3.58 (1H, dd, J=10.2, 1.8 Hz), 2.72 (1H, dd, J=18.2, 7.2 Hz), 2.50-1.60 (21H, m).

Example 4(6)

(5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-diene-19-ynoic acid

[0129]



less polar

TLC: Rf 0.26 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.84-5.66 (1H, m), 5.56-5.32 (3H, m), 4.80-3.60 (3H, br), 4.18-4.00 (1H, m), 3.77 (1H, dd, J=10.0, 2.6 Hz), 2.76 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50- 1.60 (21H, m). 1.81 (3H, t, J=2.5 Hz).

more polar

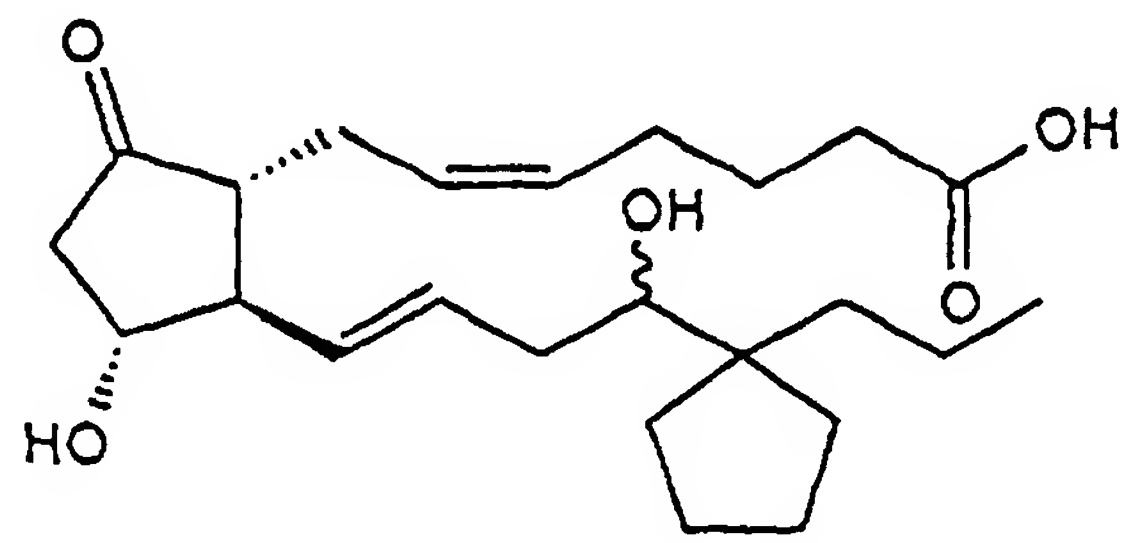
TLC: Rf 0.20 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15.0, 7.6, 5.8 Hz), 5.52-5.28 (3H, m), 5.30-4.20 (3H, br), 4.13-3.95 (1H, m), 3.72 (1H, dd, J=10.2, 2.2 Hz), 2.74 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.60 (21H, m), 1.81 (3H, t, J= 2.5 Hz).

Example 4(7)

(5Z,11α,13E)-17,17-butano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid

[0130]



less polar

TLC: Rf 0.33 (hexane ethyl acetate : acetic acid = 2 : 3 : 0.05);

NMR ($CDCl_3$) : δ 5.82-5.65 (1H, m), 5.55-5.30 (3H, m), 5.40-4.60 (3H, br), 4.16-3.98 (1H, m), 3.55 (1H, dd, J=10.6, 2.0 Hz), 2.75 (1H, dd, J=18.0, 7.0 Hz), 2.50-1.90 (11H, m), 1.80-1.10 (14H, m), 0.90 (3H, t, J=6.4 Hz).

more polar

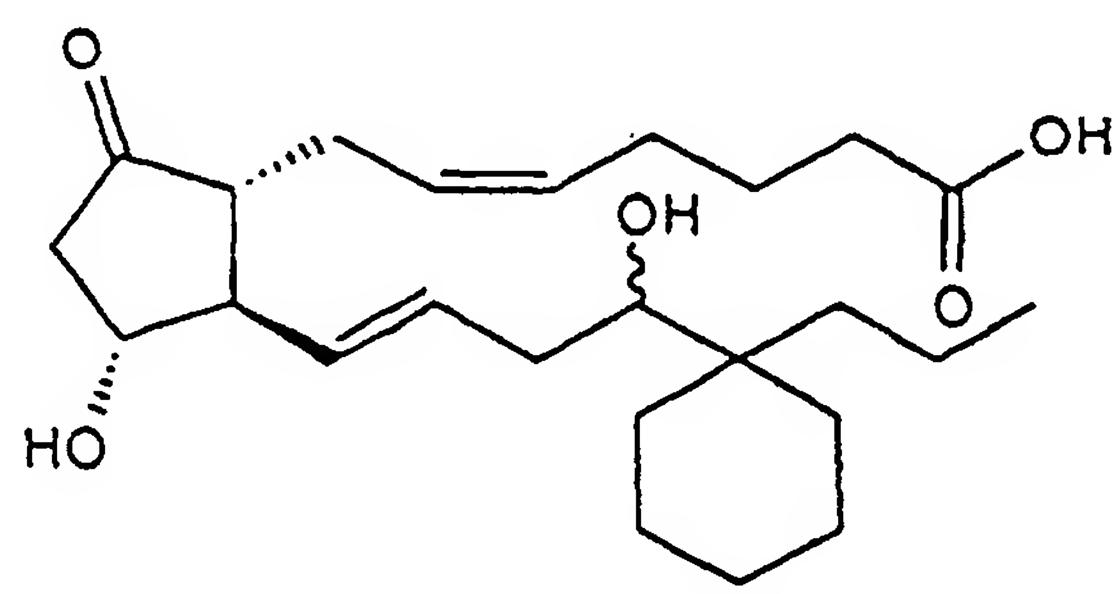
TLC: Rf 0.26 (hexane : ethyl acetate : acetic acid = 2 : 3 0.05);

NMR ($CDCl_3$) : δ 5.75-5.57 (1H, m), 5.50-5.30 (3H, m), 5.80-4.80 (3H, br), 4.12-3.94 (1H, m), 3.51 (1H, d, J= 9.4 Hz), 2.73 (1H, dd, J=18.0, 7.0 Hz), 2.50-1.95 (11H, m), 1.80-1.10 (14H, m), 0.90 (3H, t, J=6.4 Hz).

Example 4(8)

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-pentanoprosta-5,13-dienoic acid

[0131]



less polar

TLC: Rf 0.35 (hexane : ethyl acetate : acetic acid = 2 : 3 : 0.05);

NMR ($CDCl_3$) : δ 5.81-5.63 (1H, m), 5.55-5.30 (3H, m), 5.40-4.50 (3H, br), 4.15-3.98 (1H, m), 3.53 (1H, d, J= 10.2 Hz), 2.75 (1H, dd, J=18.2, 7.0 Hz), 2.50-1.90 (11H, m), 1.80-1.10 (16H, m), 0.90 (3H, t, J=6.4 Hz).

more polar

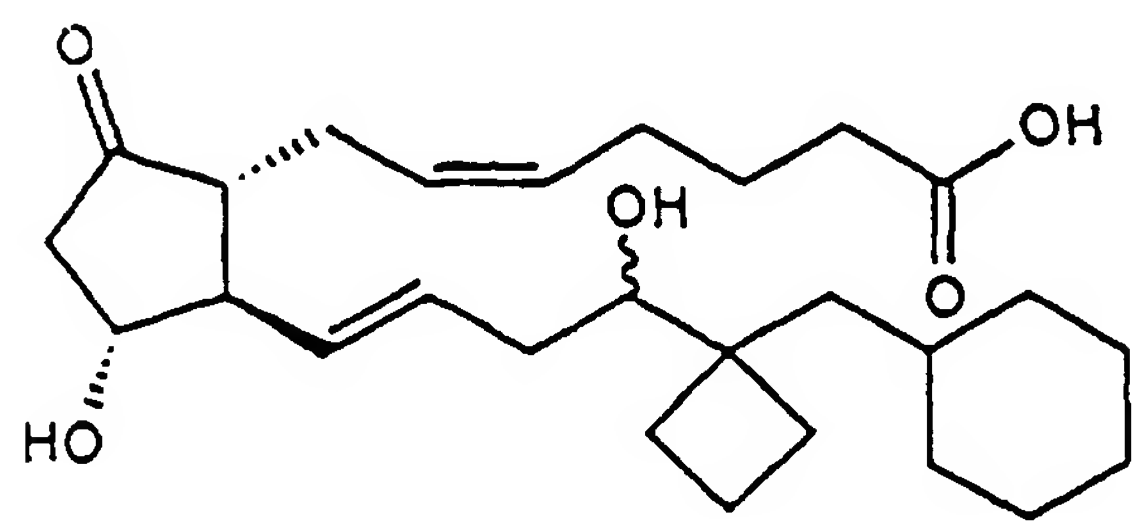
TLC: Rf 0.28 (hexane : ethyl acetate : acetic acid = 2 : 3 : 0.05);

NMR ($CDCl_3$) : δ 5.75-5.57 (1H, m), 5.50-5.30 (3H, m), 5.80-5.00 (3H, br), 4.11-3.95 (1H, m), 3.50 (1H, d, J= 10.0 Hz), 2.73 (1H, dd, J=18.4, 7.0 Hz), 2.50-1.90 (11H, m), 1.80-1.10 (16H, m), 0,90 (3H, t, J=6.4 Hz).

Example 4(9)

(5Z,11α,13E)-18-cyclohexyl-11,16-dihydroxy-9-oxo-17,17-propane-19,20-dinorprosta-5,13-dienoic acid

[0132]



less polar

TLC: Rf 0.36 (hexane : ethyl acetate : acetic acid = 1 : 2: 0.03);

NMR ($CDCl_3$) : δ 5.75 (1H, ddd, J=15.2, 7.4, 6.0 Hz), 5.55-5.30 (3H, m), 5.40-4.40 (3H, br), 4.17-4.02 (1H, m), 3.68 (1H, dd, J=10.2, 2.2 Hz), 2.76 (1H, dd, J=18.2, 7.0 Hz), 2.50-1.90 (14H, m), 1.90-1.40 (11H, m), 1.40-0.80 (7H, m). more polar

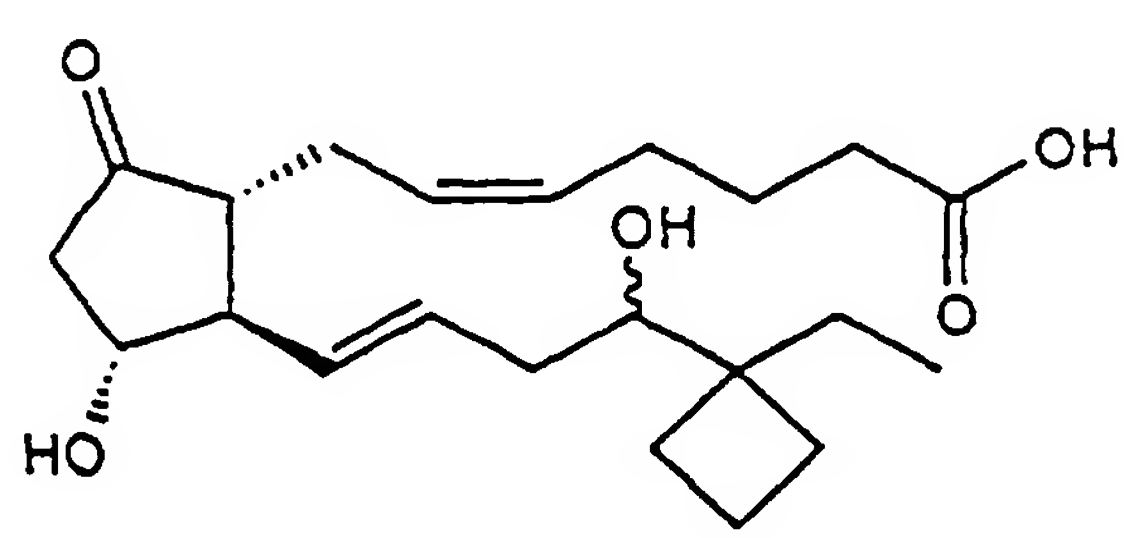
TLC: Rf 0.26 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.73 (1H, ddd, J=15.0, 7.7, 6.1 Hz), 5.55-5.30 (3H, m), 4.80-3.60 (3H, br), 4.15-3.98 (1H, m), 3.66 (1H, dd, J=10.2, 2.0 Hz), 2.74 (1H, dd, J=18.2, 6.8 Hz), 2.50-1.90 (14H, m), 1.90-1.40 (11H, m), 1.40-0.80 (7H, m).

Example 4(10)

(5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-dienoic acid

[0133]



less polar

TLC: Rf 0.43 (ethyl acetate : acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 5.73 (1H, ddd, J=16, 8, 7 Hz), 5.53-5.38 (3H, m), 4.90-4.10 (3H, brs), 4.14-4.02 (1H, m), 3.63 (1H, dd, J=10, 3 Hz), 2.75 (1H, ddd, J=19, 8, 1 Hz), 2.45-1.30 (19H, m), 2.33 (2H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz).

more polar

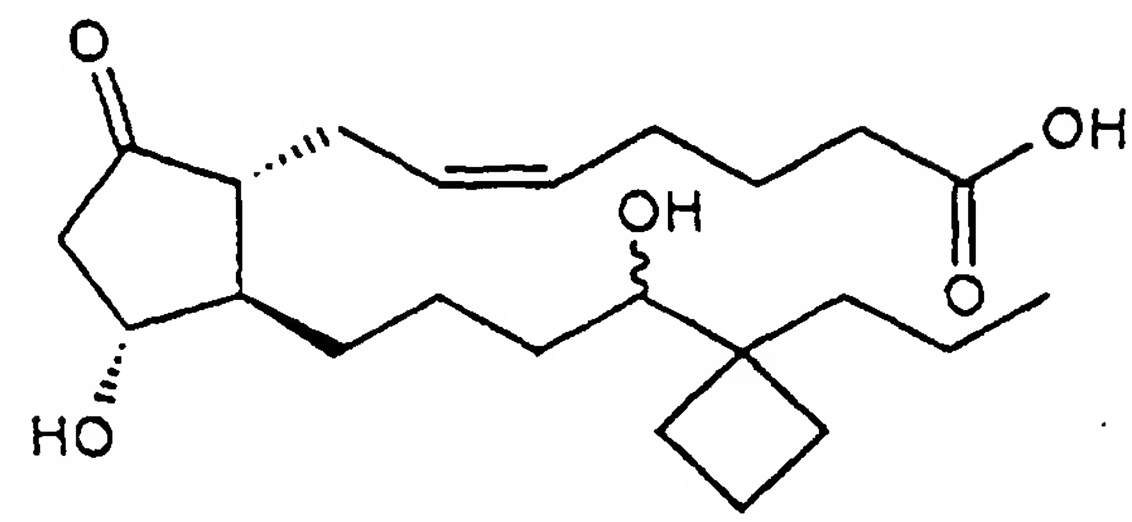
TLC: Rf 0.39 (ethyl acetate : acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15, 8, 6 Hz), 5.49-5.29 (3H, m), 5.20-4.40 (3H, brs), 4.11-3.98 (1H, m), 3.60 (1H, dd, J=10, 2 Hz), 2.73 (1H, ddd, J=18, 7, 1 Hz), 2.45-1.35 (19H, m), 2.33 (2H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz).

Example 4(11)

(5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-enoic acid

[0134]



mixture

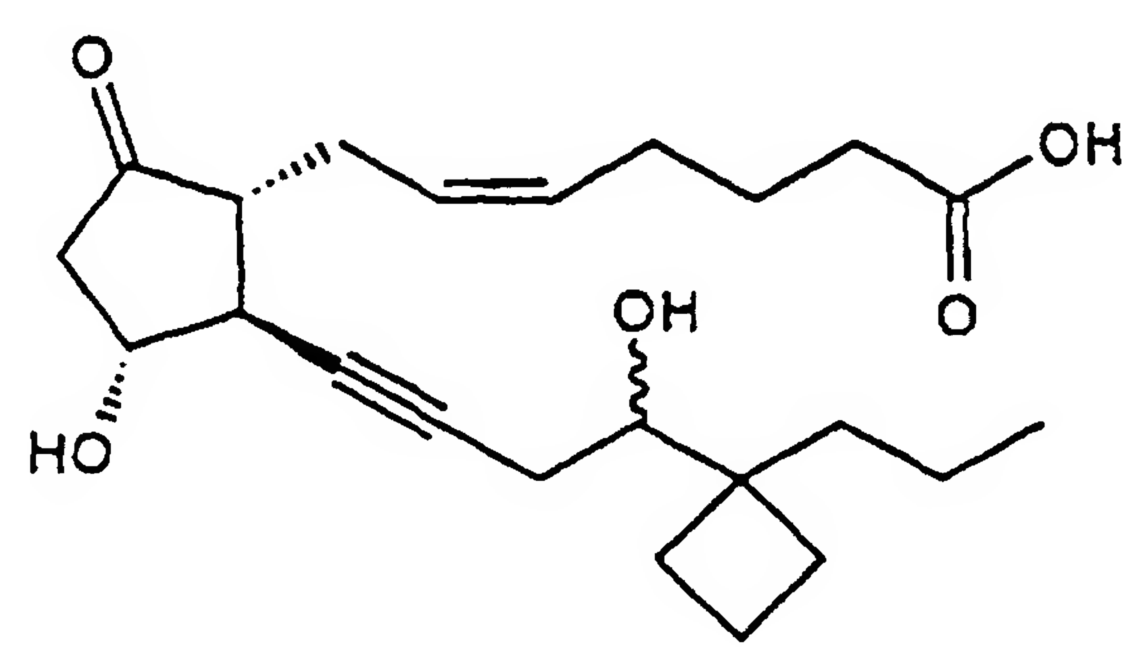
TLC: Rf 0.62 (ethyl acetate : acetic acid = 50 : 1);

NMR($CDCl_3$) : δ 5.50-5.20 (2H, m), 5.20-4.60 (3H, brs), 4.20-4.10 (1H, m), 3.58-3.52 (1H, m), 2.75-2.61 (1H, dd, J=18, 7 Hz), 2.50-1.20 (25H, m), 2.32 (2H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz).

Example 4(12)

(5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-ene-13-ynoic acid

[0135]



mixture

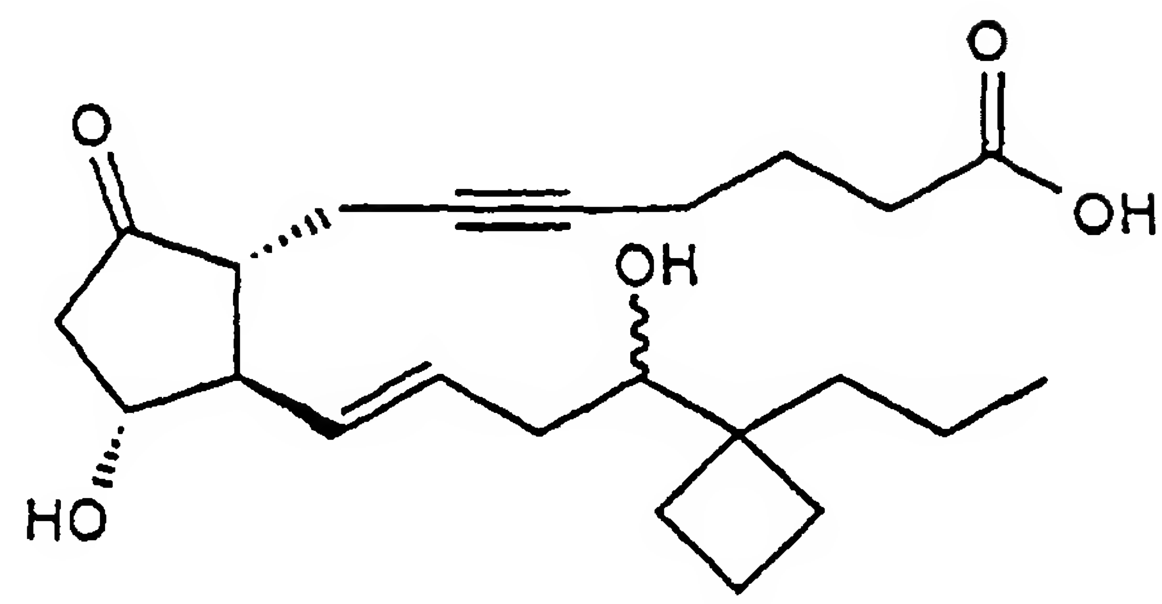
TLC: Rf 0.45 (ethyl acetate : acetic acid = 50 : 1);

NMR($CDCl_3$): δ 6.00-5.20 (3H, brs), 5.50-530 (2H, m), 4.37-4.21 (1H, m), 3.75-3.65 (1H, m), 2.73 (1H, dd, J=18.2, 6.6 Hz), 2.70-1.20 (23H, m), 0.93 (3H, t, J=7.0 Hz).

Example 4(13)

(11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-13-ene-5-ynoic acid

[0136]



less polar

TLC: Rf 0.30 (hexane : ethyl acetate : acetic acid = 1 : 3 : 0.04);

NMR($CDCl_3$) : δ 5.83 (1H, dt, J=15.4, 6.8 Hz), 5.48 (1H, dd, J=15.4, 8.2 Hz), 5.50-4.50 (3H, br), 4.22-4.05 (1H, m), 3.60 (1H, dd, J=10.0, 2.4 Hz), 2.88-2.62 (3H, m), 2.49 (2H, t, J=7.1 Hz), 2.40-1.20 (19H, m), 0.94 (3H, t, J=6.7 Hz).

more polar

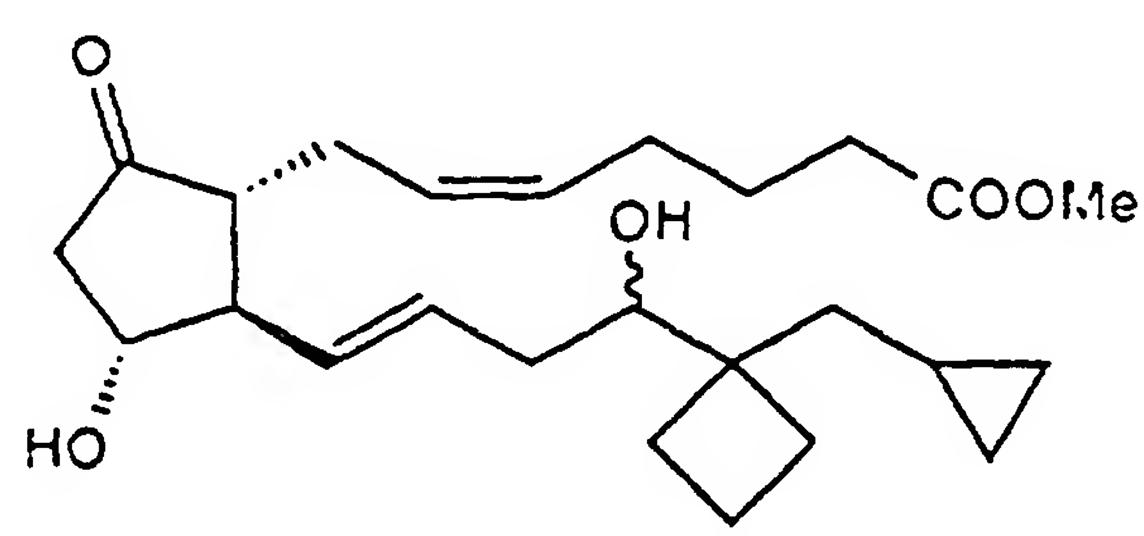
TLC: Rf 0.25 (hexane : ethyl acetate : acetic acid = 1 : 3 : 0.04);

NMR($CDCl_3$) : δ 6.00-4.80 (3H, br), 5.71 (1H, ddd, J=15.0, 9.2, 4.4 Hz), 5.41 (1H, dd, J=15.0, 8.5 Hz), 4.20-4.03 (1H, m), 3.61 (1H, d, J=10.0 Hz), 2.88-2.65 (3H, m), 2.50 (2H, t, J=7.0 Hz), 2.40-1.20 (19H, m), 0.94 (3H, t, J=6.7 Hz).

Example 5

(5Z,11α,13E)-17,17-propano-19,20-methano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester

[0137]



[0138] By the same procedure as provided in example 1, using the protected compound by TBS provided by the same procedure in reference example 1, reference example 2 or reference example 3, compounds of the present invention having the following physical data were obtained.

less polar

TLC: Rf 0.48 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.73 (1H, ddd, J=15.2, 7.8, 5.8 Hz), 5.54-5.26 (3H, m), 4.17-4.01 (1H, m), 3.74-3.63 (1H, m), 3.67 (3H, s), 2.75 (1H, ddd, J=18.4, 7.6, 1.0 Hz), 2.50-1.60 (19H, m), 2.32 (2H, t, J=7.6 Hz), 1.54 (1H, dd, J=14.0, 6.8 Hz), 1.34 (1H, dd, J=14.0, 6.4 Hz), 0.90-0.68 (1H, m), 0.55-0.44 (2H, m), 0.16-0.05 (2H, m).

more polar

TLC: Rf 0.38 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.70 (1H, ddd, J=15.4, 8.2, 5.6 Hz), 5.50-5.25 (3H, m), 4.14-3.98 (1H, m), 3.74-3.62 (1H, m),

3.67 (3H, s), 3.34 (1 H, br), 2.74 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.60 (18H, m), 2.31 (2H, t, J=7.4 Hz), 1.53 (1H, dd, J=14.0, 6.8 Hz), 1.36 (1H, dd, J=14.0, 6.4 Hz), 0.90-0.68 (1H, m), 0.56-0.45 (2H, m), 0.16-0.06 (2H, m).

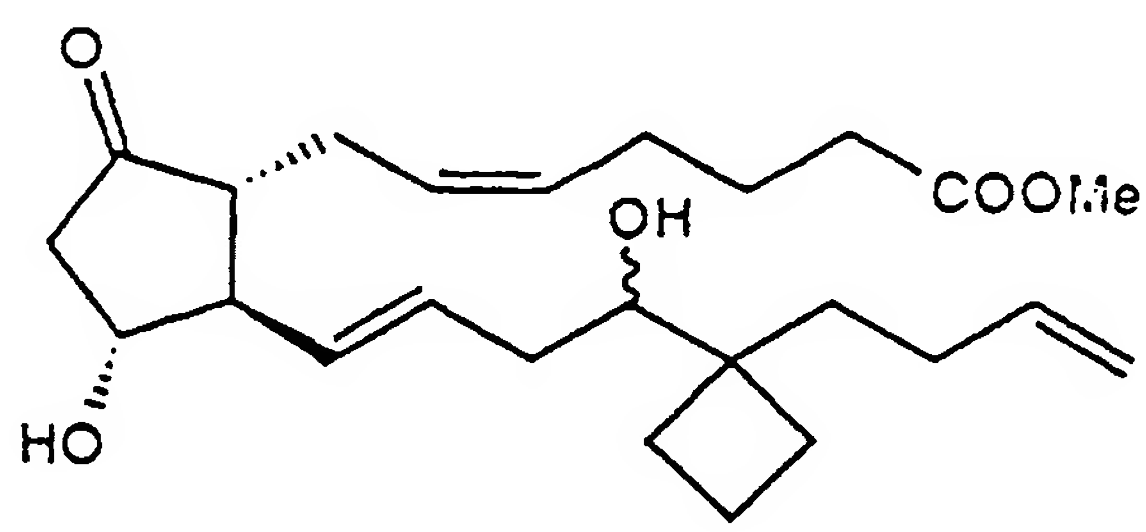
Example 5(1)~5(7)

[0139] By the same procedure as provided in example 5, compounds of the present invention having the following physical data were obtained.

Example 5(1)

(5Z,11α,13E)-17,17-propano-20,20-methylene-11,16-dihydroxy-9-oxoprosta-5,13-diencic acid · methylester

[0140]



less polar

TLC: Rf 0.49 (Hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.86 (1H, ddt, J=17.0, 10.4, 6.5 Hz), 5.71 (1H, ddd, J=15.2, 7.8, 5.8 Hz), 5.55-5.25 (3H, m), 5.10-4.90 (2H, m), 4.18-4.01 (1H, m), 3.67 (3H, s), 3.57 (1H, dd, J=10.0, 2.6 Hz), 2.76 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.40 (23H, m), 2.32 (2H, t, J=7.4 Hz).

more polar

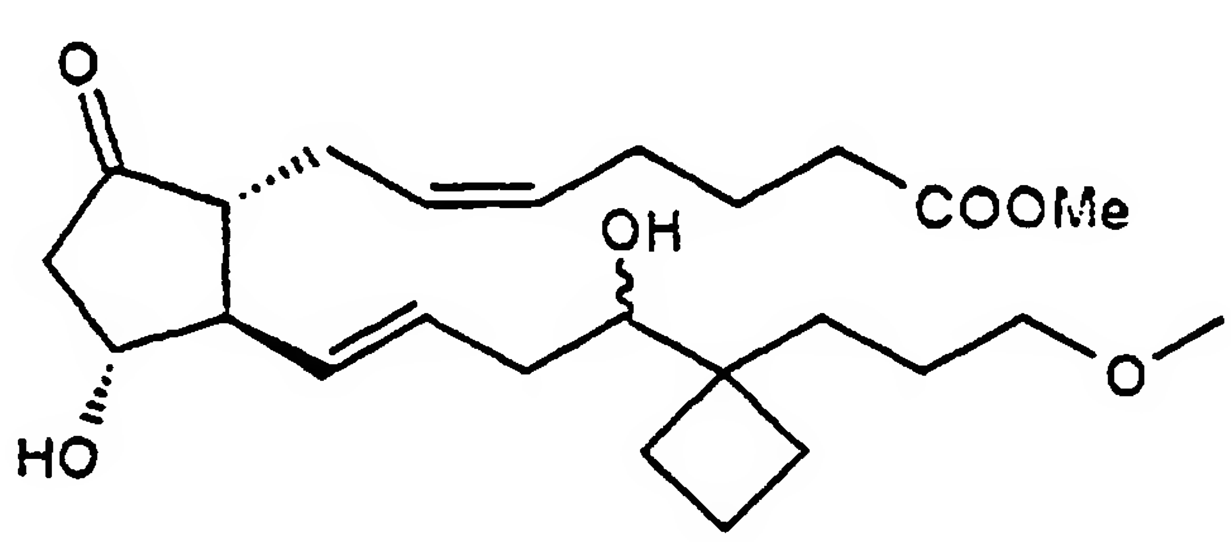
TLC: Rf 0.40 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.86 (1H, ddt, J=17.2, 10.2, 6.4 Hz), 5.71 (1H, ddd, J=15.2, 8.0, 5.8 Hz), 5.50-5.25 (3H, m), 5.10-4.90 (2H, m), 4.14-3.98 (1H, m), 3.67 (3H, s), 3.57 (1H, dd, J=10.2, 2.4 Hz), 3.02 (1H, br), 2.74 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.40 (22H, m), 2.32 (2H, t, J=7.5 Hz).

Example 5(2)

(5Z,11α,13E)-17,17-propano-20-methoxy-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester

[0141]



less polar

TLC: Rf 0.25 (hexane : ethyl acetate = 1 : 3);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15.4, 7.4, 6.4 Hz), 5 53-5.25 (3H, m), 4.15-4.00 (1H, m), 3.67 (3H, s), 3.57

(1H, dd, J=9.6, 2.6 Hz), 3.48-3.30 (2H, m), 3.35 (3H, s), 2.75 (1H, ddd, J=18.4, 8.0, 1.0 Hz), 2.70 (1H, br), 2.50-1.45 (22H, m), 2.32 (2H, t, J=7.5 Hz).

more polar

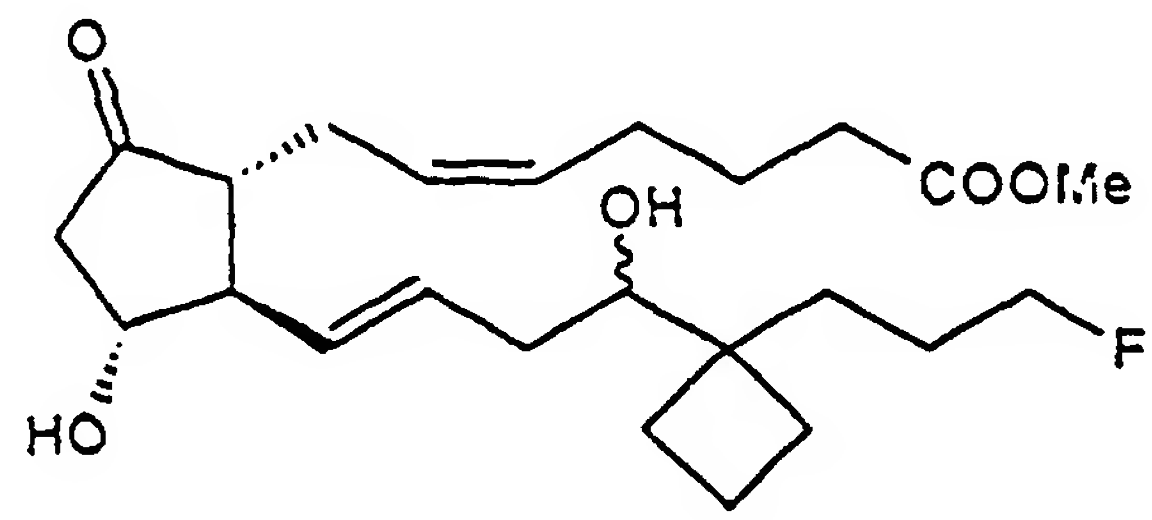
TLC: Rf 0.17 (hexane : ethyl acetate = 1 : 3);

NMR ($CDCl_3$) : δ 5.69 (1H, ddd, J=15.2, 8.4, 5.6 Hz), 5.50-5.25 (3H, m), 4.13-3.98 (1H, m), 3.67 (3H, s), 3.56 (1H, dd, J=10.0, 2.2 Hz), 3.46-3.32 (2H, m), 3.35 (3H, s), 2.74 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.45 (23H, m), 2.31 (2H, t, J=7.3 Hz).

Example 5(3)

(5Z,11α,13E)-17,17-propano-20-fluoro-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester

[0142]



less polar

TLC: Rf 0.31 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.71 (1H, ddd, J=15.4, 7.6, 5.8 Hz), 5.55-5.25 (3H, m), 4.47 (2H, dt, J=47.0, 5.2 Hz). 4.17-4.02 (1H, m), 3.67 (3H, s), 3.58 (1H, dd, J=10.0, 2.4 Hz), 2.76 (1H, ddd, J=18.6, 7.4, 1.2 Hz), 2.50-1.40 (23H, m), 2.32 (2H, t, J=7.3 Hz). more polar

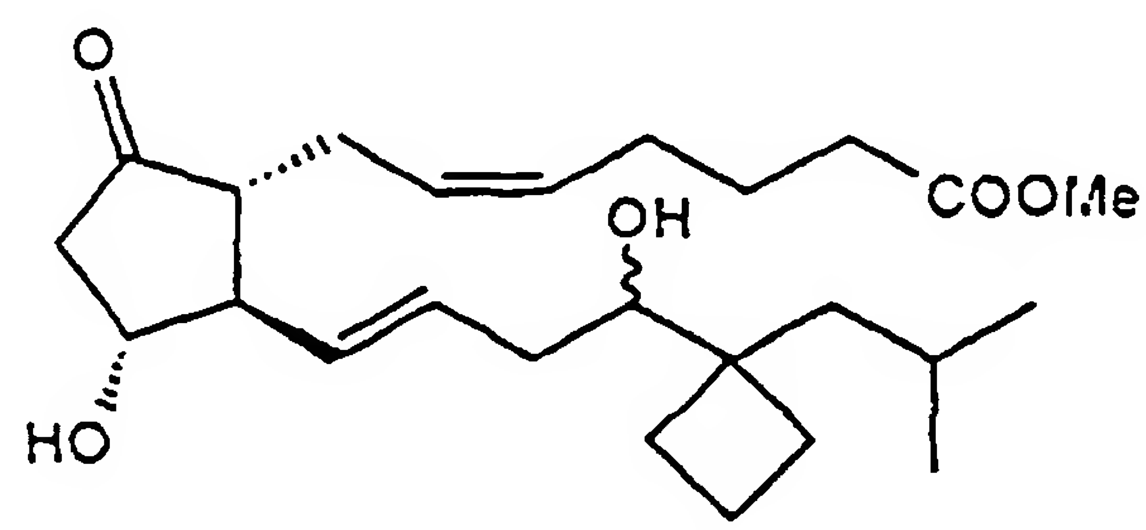
TLC: Rf 0.24 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.70 (1 H, ddd, J=15.4, 8.2, 5.8 Hz), 5.52-5.25 (3H, m), 4.47 (2H, dt, J=46.8, 5.8 Hz), 4.14-3.98 (1H, m), 3.67 (3H, s), 3.58 (1H, dd, J=10.2, 2.2 Hz), 3.06 (1H, br), 2.74 (1H, ddd, J=18.4, 7.4, 1.0 Hz), 2.50-1.40 (22H, m), 2.32 (2H, t, J=7.5 Hz).

Example 5(4)

(5Z,11α,13E)-17,17-propano-19-methyl-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester

[0143]



less polar

TLC: Rf 0.45 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.73 (1H, ddd, J=15.2, 8.0, 6.0 Hz), 5.50-5.25 (3H, m), 4.17-4.02 (1H, m), 3.70-3.58 (1H, m), 3.67 (3H, s), 2.76 (1H, ddd, J=18.4, 7.6, 1.0 Hz), 2.50-1.60 (20H, m), 2.33 (2H, t, J=7.4 Hz), 1.56 (1H, dd, J=14.2, 6.8

Hz), 1.33 (1H, dd, J=14.2, 6.2 Hz), 0.92 (6H, d, J=6.6 Hz).
more polar

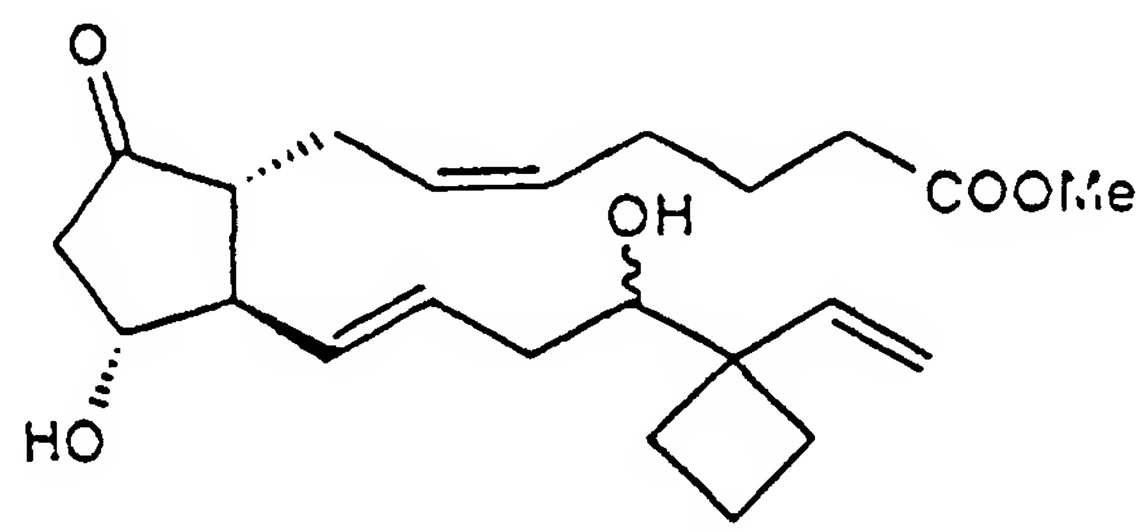
TLC: Rf 0.35 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.72 (1H, ddd, J=15.2, 8.2, 5.8 Hz), 5.50-5.25 (3H, m), 4.14-3.98 (1H, m), 3.70-3.59 (1H, m), 3.67 (3H, s), 3.24 (1H, br), 2.74 (1H, ddd, J=18.4, 7.6, 1.0 Hz), 2.50-1.60 (19H, m), 2.32 (2H, t, J=7.4 Hz), 1.56 (1H, dd, J=14.2, 6.8 Hz), 1.34 (1H, dd, J=14.2, 6.4 Hz), 0.92 (6H, d, J=6.6 Hz).

Example 5(5)

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-20-norprosta-5,13,18-trienoic acid · methylester

[0144]



less polar

TLC: Rf 0.30 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$): δ 5.95 (1H, dd, J=17.2, 10.7 Hz), 5.69 (1H, ddd, J=15.2, 7.6, 6.0 Hz), 5.49-5.29 (3H, m), 5.22 (1H, dd, J=10.7, 1.8 Hz), 5.15 (1H, dd, J=17.2, 1.8 Hz), 4.13-4.01 (1H, m), 3.67 (3H, s), 3.60 (1H, dd, J=10.0, 2.3 Hz), 2.74 (1H, ddd, J=18.4, 7.4, 1.2 Hz), 2.45-1.60 (19H, m), 2.30 (2H, t, J=7.0 Hz).
more polar

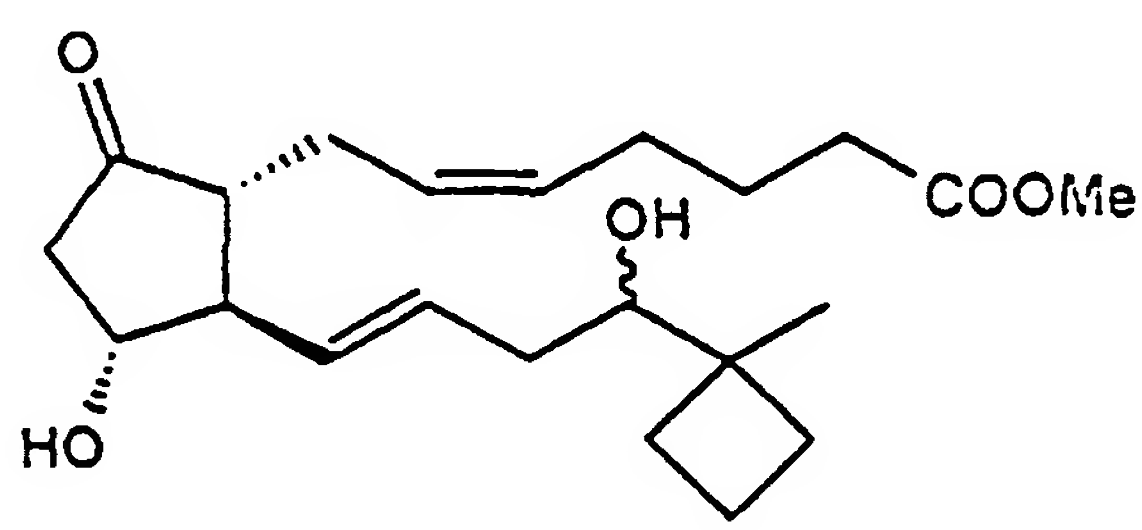
TLC: Rf 0.22 (hexane : ethyl acetate = 1 : 2);

NMR ($CDCl_3$) : δ 5.94 (1H, dd, J=17.0, 10.8 Hz), 5.67 (1H, ddd, J=15.2, 8.4, 5.8 Hz), 5.45-5.29 (3H, m), 5.23 (1H, dd, J=10.8, 1.6 Hz), 5.15 (1H, dd, J=17.0, 1.8 Hz), 4.13-3.97 (1H, m), 3.66 (3H, s), 3.59 (1H, dd, J=10.4, 2.2 Hz), 2.73 (1H, dd, J=18.2, 7.2 Hz), 2.44-1.60 (19H, m), 2.30 (2H, t, J=6.9 Hz).

Example 5(6)

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-19,20-dinorprosta-5,13-dienoic acid · methylester

[0145]



more polar

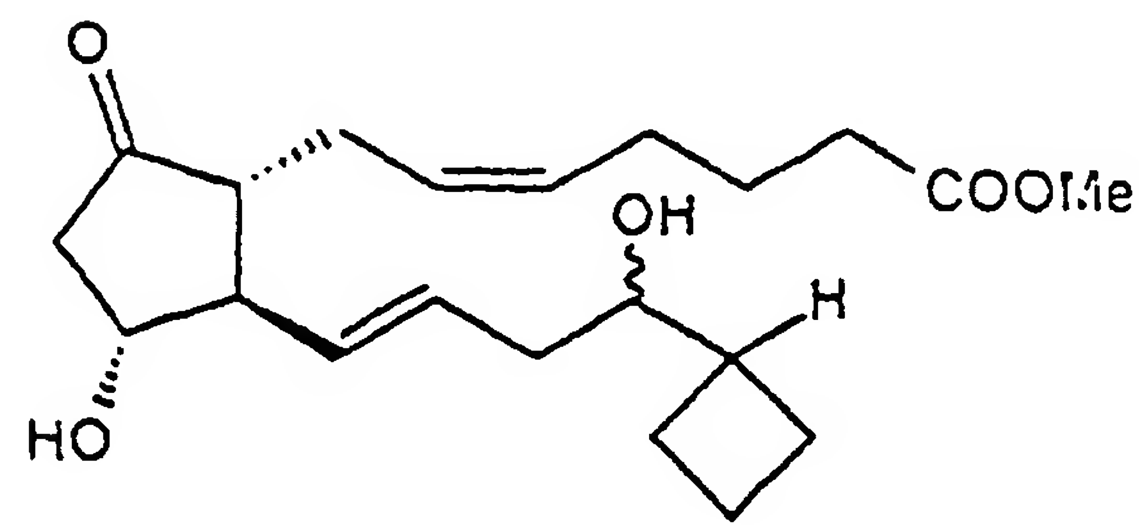
TLC: Rf 0.30 (hexane : ethyl acetate = 1 : 3);

NMR($CDCl_3$) : δ 5.71 (1H, ddd, J=15, 8, 6Hz), 5.55-5.25 (3H, m), 4.18-4.02 (1H, m), 3.67 (3H, s), 3.56 (1H, dd, J=10, 2Hz), 2.73 (1H, ddd, J=19, 7, 1Hz), 2.50-1.60 (21H, m), 1.15 (3H, s)

Example 5(7)

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-16,19,20-trinorprosta-5,13-dienoic acid · methylester

[0146]



more polar

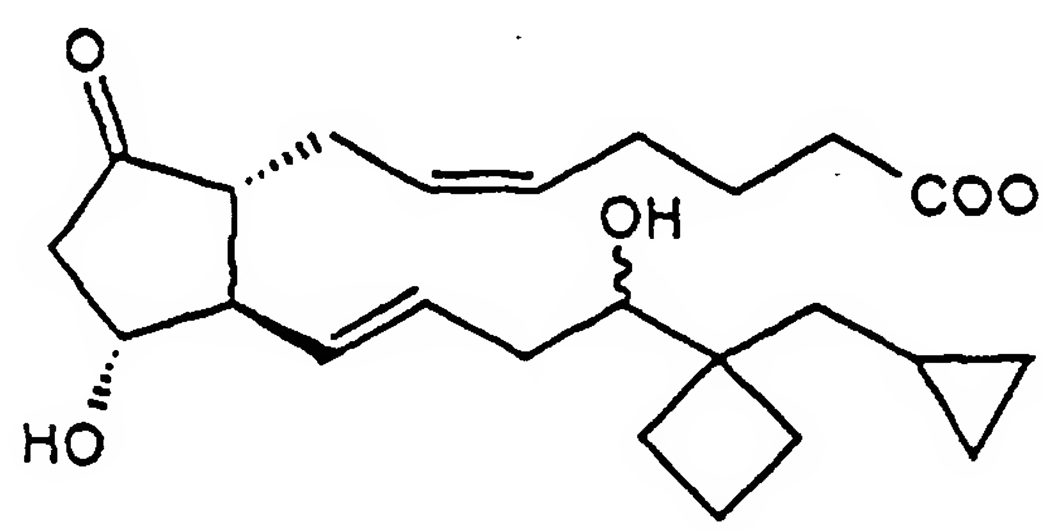
TLC: Rf 0.25 (hexane : ethyl acetate = 1 : 3);

NMR ($CDCl_3$) : δ 5.70 (1H, ddd, J=15, 8, 6Hz), 5.54-5.26 (3H, m), 4.17-4.00 (1H, m), 3.66 (3H, s), 3.62-3.50 (1H, m), 2.74 (1H, ddd, J=18, 7, 1Hz), 2.60-1.60 (22H, m).

Example 6

(5Z,11α,13E)-17,17-propano-19,20-methano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid

[0147]



[0148] By the same procedure as provided in example 4, using each obtained the compound prepared in example 5, compounds of the present invention having the following physical data were obtained.

less polar

TLC: Rf 0.31 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.83-5.66 (1H, m), 5.60-5.30 (3H, m), 5.40-4.20 (3H, br), 4.17-4.00 (1H, m), 3.77 (1H, dd, J=10.4, 2.2 Hz), 2.75 (1H, dd, J=18.4, 7.6 Hz), 2.50-1.60 (19H, m), 1.53 (1H, dd, J=14.2, 6.7 Hz), 1.35 (1H, dd, J=14.2, 6.4 Hz), 0.95-0.65 (1H, m), 0.60-0.45 (2H, m), 0.20-0.05 (2H, m).

more polar

TLC: Rf 0.26 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 6.00-4.00 (3H, br), 5.70 (1H, ddd, J=15.4, 7.8, 5.6 Hz), 5.50-5.25 (3H, m), 4.14-3.96 (1 H, m), 3.73 (1H, dd, J=10.0, 2.0 Hz), 2.74 (1H, dd, J=18.4, 7.6 Hz), 2.50-1.60 (19H, m), 1.50 (1H, dd, J=14.2, 6.8 Hz), 1.37 (1H, dd, J=14.2, 6.3 Hz), 0.90-0.70 (1H, m), 0.60-0.45 (2H, m), 0.17-0.05 (2H, m).

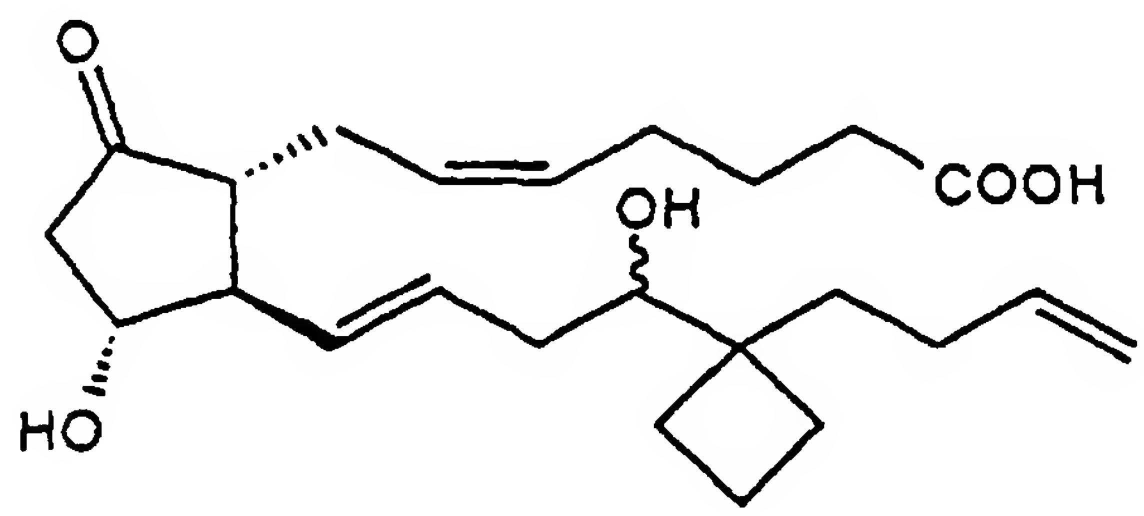
Example 6(1)~6(8)

[0149] By the same procedure as provided in example 6, compounds of the present invention having the following physical data were obtained.

Example 6(1)

(5Z,11α,13E)-17,17-propano-20,20-methylene-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid

[0150]



less polar

TLC: Rf 0.32 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.86 (1H, ddt, J=17.0, 10.2, 6.8 Hz), 5.80-5.64 (1H, m), 5.55-5.30 (3H, m), 5.10-4.90 (2H, m), 5.00-4.00 (3H, br), 4.16-4.00 (1H, m), 3.64 (1H, dd, J=10.2, 2.4 Hz), 2.75 (1H, dd, J=18.4, 7.4 Hz), 2.50-1.40 (23H, m).

more polar

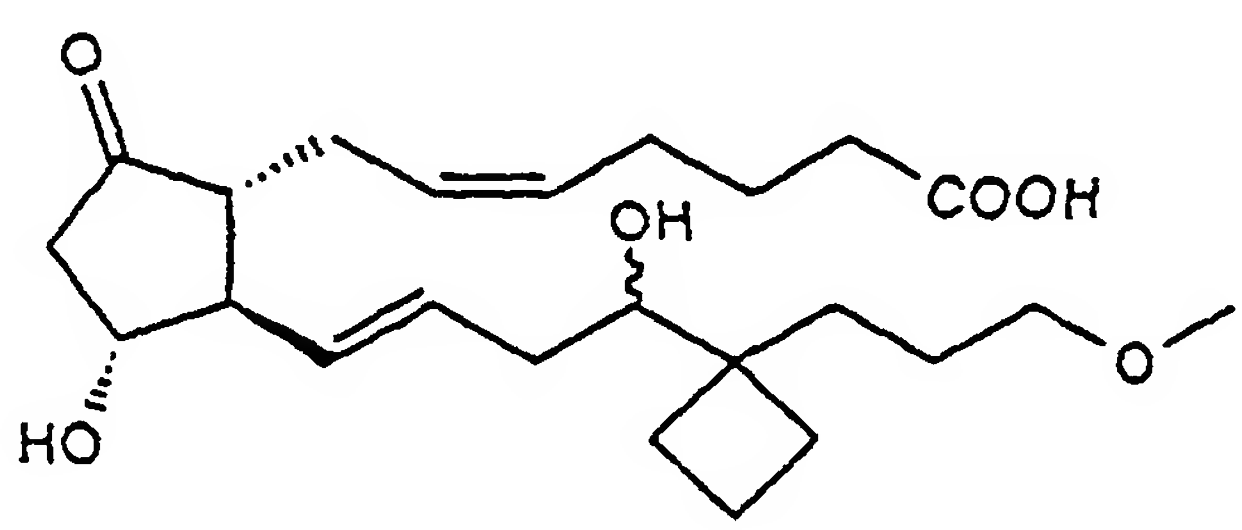
TLC: Rf 0.27 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.86 (1H, ddt, J=17.0, 10.2, 6.4 Hz), 5.78-5.60 (1H, m), 5.60-4.40 (3H, br), 5.55-5.25 (3H, m), 5.10-4.90 (2H, m), 4.12-3.96 (1H, m), 3.61 (1H, dd, J=10.2, 1.8 Hz), 2.74 (1H, dd, J=18.6, 7.4 Hz), 2.50-1.40 (23H, m).

Example 6(2)

(5Z,11α,13E)-17,17-propano-20-methoxy-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid

[0151]



less polar

TLC: Rf 0.36 (ethyl acetate : acetic acid = 100 : 1);

NMR ($CDCl_3$) : δ 5.72 (1H, dt, J=15.2, 6.6 Hz), 5.55-5.25 (3H, m), 5.60-4.40 (3H, br), 4.16-4.00 (1H, m), 3.61 (1H, dd, J=9.6, 2.2 Hz), 3.48-3.38 (2H, m), 3.37 (3H, s), 2.75 (1H, dd, J=18.2, 7.4 Hz), 2.50-1.40. (23H, m).

more polar

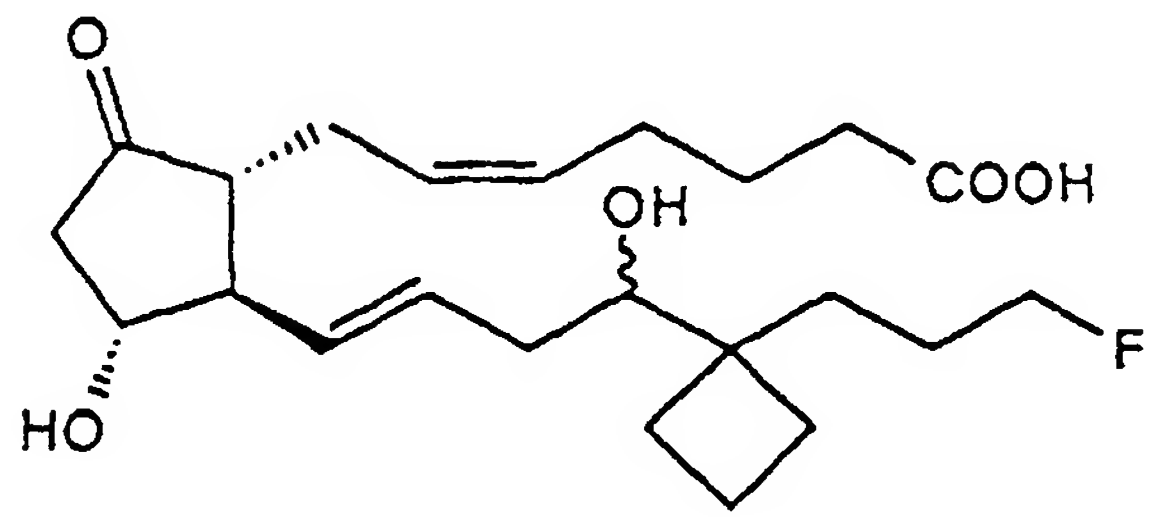
TLC: Rf 0.27 (ethyl acetate : acetic acid = 100 : 1);

NMR ($CDCl_3$) : δ 5.68 (1H, ddd, J=15.2, 8.0, 5.0 Hz), 5.50-5.20 (3H, m), 5.40-4.20 (3H, br), 4.13-3.97 (1H, m), 3.56 (1H, dd, J=10.4, 2.0 Hz), 3.55-3.35 (2H, m), 3.36 (3H, s), 2.75 (1H, dd, J=18.2, 7.4 Hz), 2.50-1.40 (23H, m).

Example 6(3)

(5Z,11α,13E)-17,17-propano-20-fluoro-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid

[0152]



less polar

TLC: Rf 0.30 (hexane : ethyl acetate : acetic acid = 1 : 3 : 0.04);

NMR ($CDCl_3$) : δ 5.72 (1H, ddd, J=15.5, 7.0, 6.0 Hz), 5.48 (1H, dd, J=15.5, 8.5 Hz), 5.46-5.36 (2H, m), 5.20-3.80 (3H, br), 4.55-4.48 and 4.46-4.38 (2H, m), 4.12-4.04 (1H, m), 3.64 (1H, dd, J=10.5, 2.0 Hz), 2.75 (1H, ddd, J=18.5, 7.5, 1.0 Hz), 2.43-2.26 (6H, m). 2.21 (1H, dd, J=18.5, 10.0 Hz), 2.15-1.95 (6H, m), 1.95-1.63 (9H, m), 1.57-1.48 (1H, m).

more polar

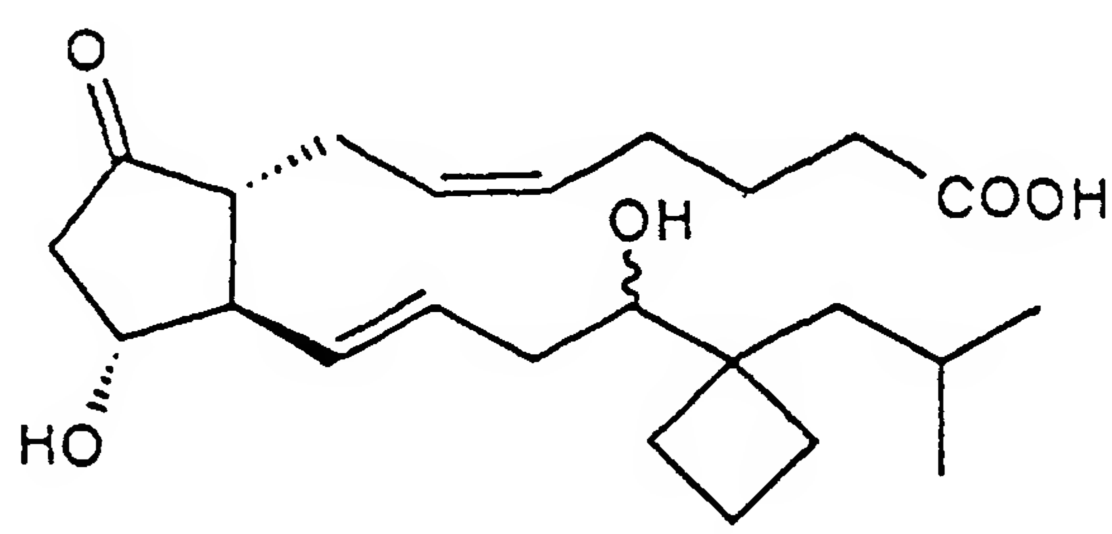
TLC: Rf 0.23 (hexane : ethyl acetate : acetic acid = 1 : 3 : 0.04);

NMR ($CDCl_3$) : δ 5.68 (1H, ddd, J=15.5, 8.0, 5.5 Hz), 5.46 (1H, dd, J=15.5, 8.5 Hz), 5.50-4.50 (3H, br), 5.45-5.33 (2H, m), 4.55-4.48 and 4.46-4.38 (2H, m), 4.10-4.02 (1H, m), 3.61 (1H, dd, J=10.5, 2.0 Hz), 2.73 (1H, dd, J=18.0, 7.0 Hz), 2.43-2.25 (6H, m), 2.20 (1H, dd, J=18.0, 10.0 Hz), 2.15-1.95 (6H, m), 1.95-1.62 (9H, m), 1.57-1.48 (1H, m).

Example 6(4)

(5Z,11α,13E)-17,17-propano-19-methyl-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid

[0153]



less polar

TLC: Rf 0.31 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.75 (1H, dt, J=15.2, 6.4 Hz), 5.55-5.30 (3H, m), 5.40-4.40 (3H, br), 4.17-4.00 (1H, m), 3.70 (1H, dd, J=10.2, 2.0 Hz), 2.76 (1H, ddd, J=18.6, 7.4, 1.0 Hz), 2.50-1.50 (20H, m), 1.55 (1H, dd, J=14.2, 6.8 Hz), 1.33 (1H, dd, J=14.2, 6.2 Hz), 0.92 (6H, d, J=6.6 Hz).

more polar

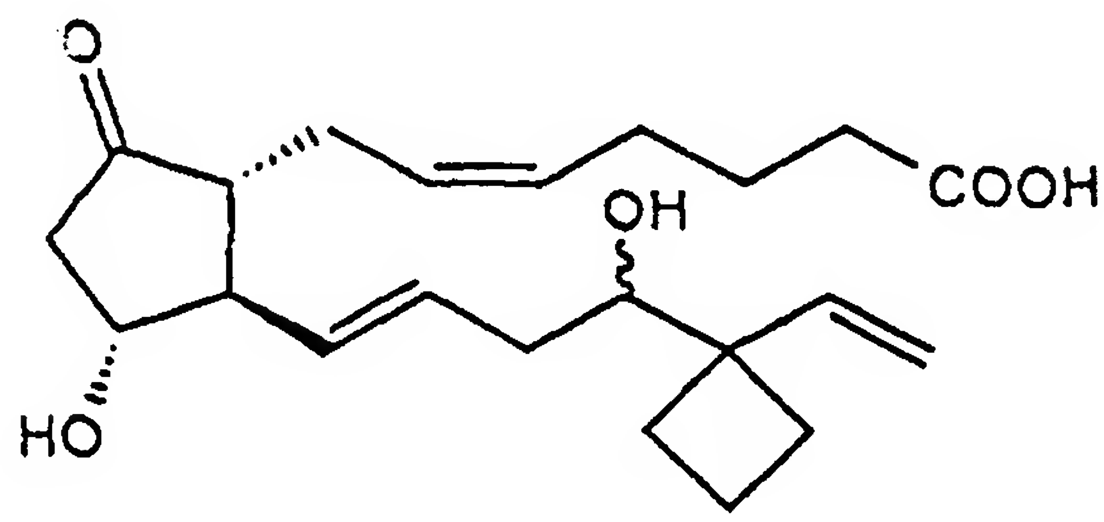
TLC: Rf 0.24 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.72 (1H, ddd, J=15.2, 8.0, 5.8 Hz), 5.55-5.25 (3H, m), 5.20-4.20 (3H, br), 4.14-3.96 (1H, m), 3.68 (1H, dd, J=10.0, 2.0 Hz), 2.74 (1H, ddd, J=18.0, 7.2, 1.0 Hz), 2.50-1.50 (20H, m), 1.55 (1H, dd, J=14.2, 7.2 Hz), 1.33 (1H, dd, J=14.2, 6.4 Hz), 0.92 (6H, d, J=6.4 Hz).

Example 6(5)

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-20-norprosta-5,13,18-trienoic acid

[0154]



less polar

TLC: Rf 0.36 (ethyl acetate : acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 5.93 (1H, dd, J=17.2, 10.6 Hz), 5.70 (1H, ddd, J=15.2, 7.2, 5.8 Hz), 5.49-5.38 (3H, m), 5.24 (1H, dd, J=10.6, 1.4 Hz), 5.16 (1H, dd, J=17.2, 1.4 Hz), 4.20-3.20 (3H, br), 4.13-4.00 (1H, m), 3.68 (1H, dd, J=10.4, 2.4 Hz), 2.74 (1H, ddd, J=18.4, 7.4, 1.2 Hz), 2.43-1.60 (19H, m).

more polar

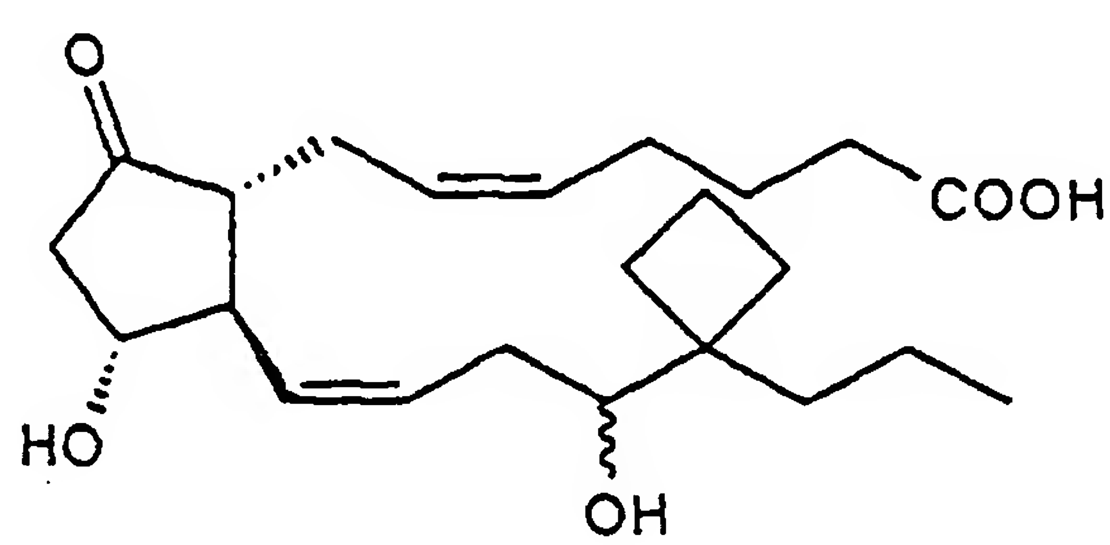
TLC: Rf 0.32 (ethyl acetate : acetic acid = 50 : 1);

NMR ($CDCl_3$) : δ 5.93 (1H, dd, J=17.2, 10.6 Hz), 5.65 (1H, ddd, J=15.2, 8.2, 5.6 Hz), 5.28-5.15 (3H, m), 5.25 (1H, dd, J=10.6, 1.4 Hz), 5.16 (1H, dd, J=17.2, 1.4 Hz), 5.10-4.10 (2H, br), 4.08-3.95 (1H, m), 3.63 (1H, dd, J=10.6, 2.0 Hz), 2.70 (1H, ddd, J=19.2, 7.6, 1.1 Hz), 2.42-1.60 (19H, m).

Example 6(6)

(5Z,11α,13Z)-17,17-propano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid

[0155]



less polar

TLC: Rf 0.49 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 6.00-4.00 (3H, br), 5.67 (1H, dt, J=5, 11 Hz), 5.46 (1H, t, J=11 Hz), 5.43-5.33 (2H, m), 4.08-4.00 (1H, m), 3.61 (1H, dd, J=10, 2 Hz), 2.83-2.72 (2H, m), 2.40-2.25 (3H, m), 2.33 (2H, t, J=7.5 Hz), 2.25 (1H, dd, J=19, 9.5 Hz), 2.15-2.03 (4H, m), 2.03-1.63 (8H, m), 1.60-1.53 (1H, m), 1.43-1.25 (3H, m), 0.05 (3H, t, J=7 Hz).

more polar

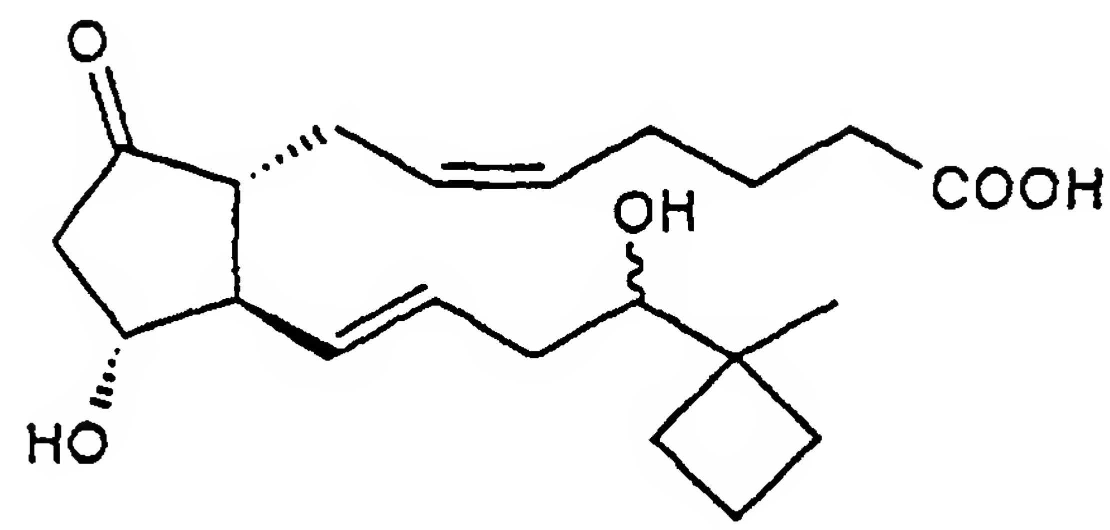
TLC: Rf 0.45 (hexane : ethyl acetate : acetic acid = 1 : 2 : 0.03);

NMR ($CDCl_3$) : δ 5.69 (1H, dt, J=11,8 Hz), 5.47-5.35 (3H, m), 5.00-3.00 (3H, br), 4.10-4.03 (1H, m), 3.64 (1H, dd, J=7, 3 Hz), 2.84-2.73 (2H, m), 2.43-1.95 (9H, m), 2.33 (2H, t, J=7 Hz), 2.26 (1H, dd. J=18.5, 9.5 Hz). 1.92-1.55 (7H, m), 1.45-1.30 (3H, m), 0.95 (3H, t, J=7 Hz).

Example 6(7)

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-19,20-dinorprosta-5,13-dienoic acid

[0156]



more polar

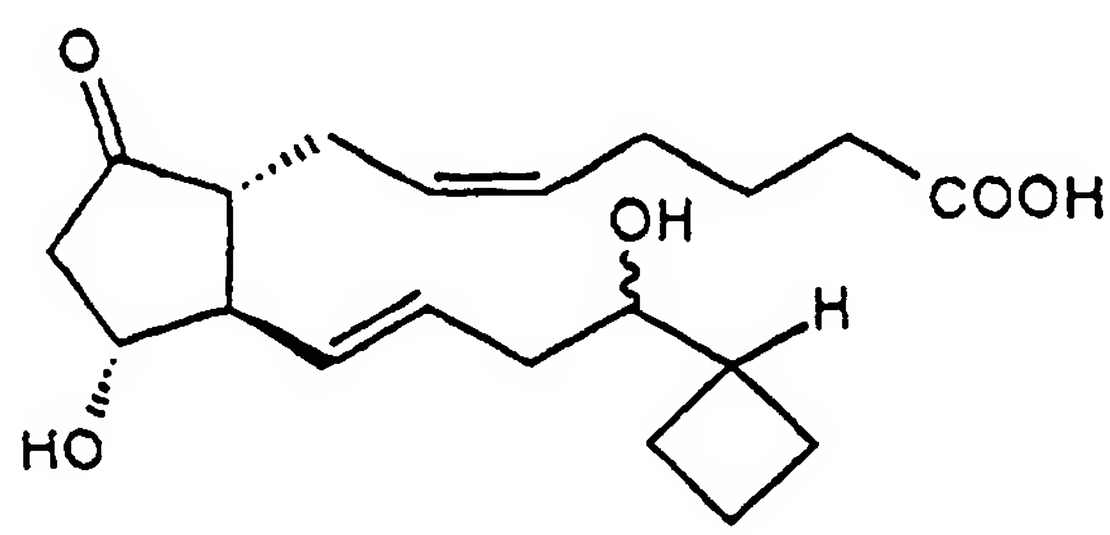
TLC: Rf 0.19 (hexane : ethyl acetate : acetic acid = 1 : 3 : 0.04);

NMR ($CDCl_3$) : δ 6.00-4.00 (3H, br), 5.71 (1H, ddd, J=15, 8, 6Hz), 5.55-5.30 (3H, m), 4.15-3.95(1H, m), 3.60 (1H, dd, J=10, 2Hz), 2.73 (1H, ddd, J=18, 7, 1Hz), 2.50-1.60 (19H, m), 1.15 (3H, s).

Example 6(8)

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-18,19,20-trinorprosta-5,13-dienoic acid

[0157]



more polar

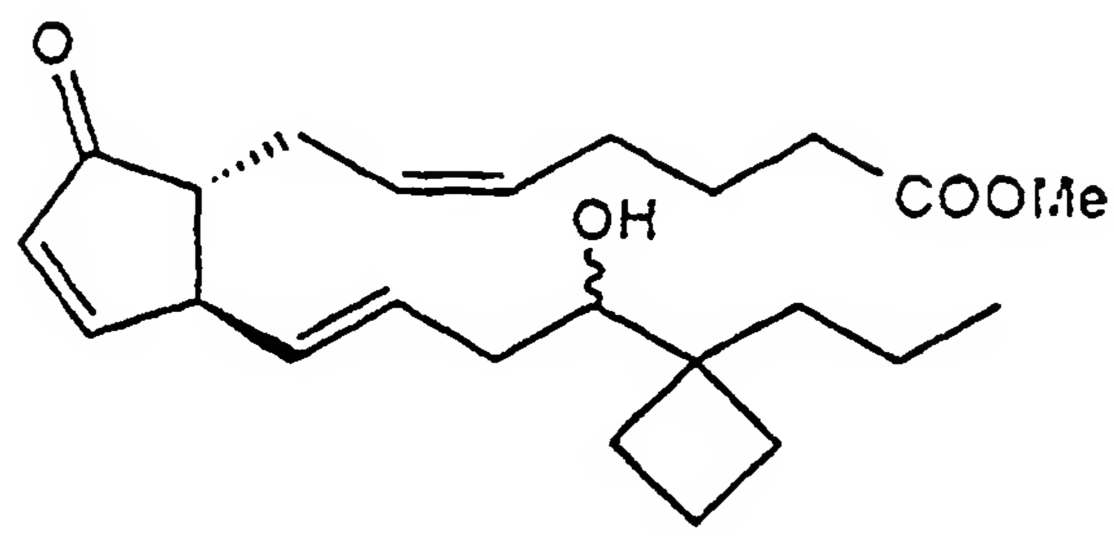
TLC: Rf 0.16 (hexane : ethyl acetate : acetic acid = 1 : 3 : 0.04);

NMR ($CDCl_3$) : δ 6.00-4.00 (3H, br), 5.70 (1H, ddd, J=15, 8, 6Hz), 5.53-5.28 (3H, m), 4.13-3.96 (1H, m), 3.65-3.55 (1H, m), 2.74 (1H, ddd, J=18, 7, 1Hz), 2.60-1.60 (20H, m)

Reference example 12

(5Z,13E)-17,17-propano-16-hydroxy-9-oxoprosta-5,10,13-trienoic acid · methylester

[0158]



[0159] To a solution of the compound prepared in example 1 (more polar; 95 mg) in THF (5 ml) was added copper chloride (40 mg) and 1N aqueous solution of hydrochloric acid (5 ml). The reaction mixture was stirred at 60 °C for 4 hours. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium hydrogencarbonate, extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. To the residue dissolved into diethyl ether (5 ml) was added a solution of diazomethane in diethyl ether until the reaction solution became yellow color. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate) to give the title compound (65 mg) having the following physical data.

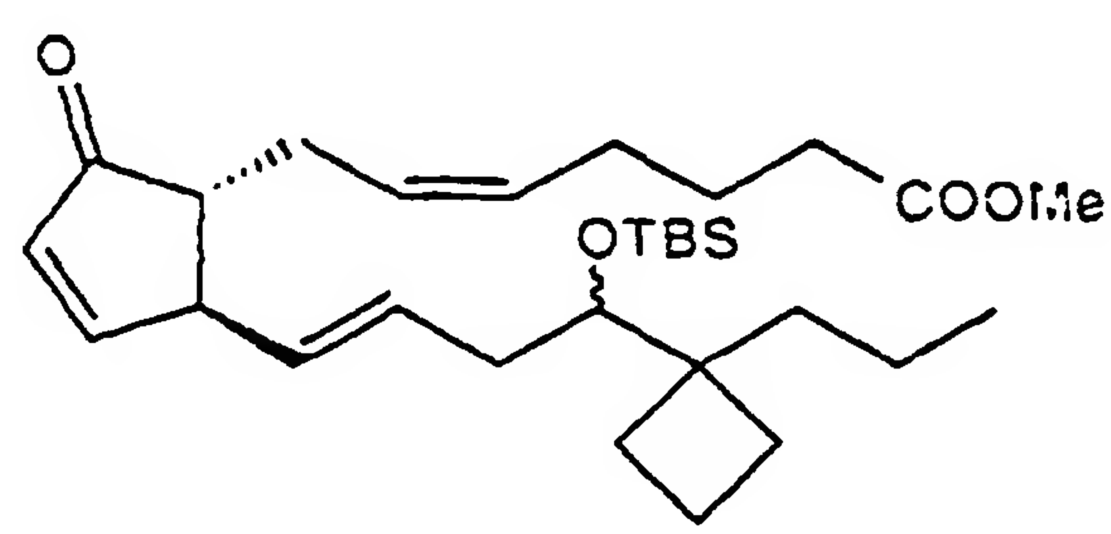
TLC: Rf 0.68 (hexane : ethyl acetate = 1 : 1).

NMR ($CDCl_3$) : δ 7.49 (1H, dd, J = 6.0, 2.8 Hz), 6.16 (1H, dd, J = 6.0, 2.2 Hz), 5.67-5.24 (4H, m), 3.67 (3H, s), 3.54 (1H, dd, J = 9.8, 2.8 Hz), 3.25-3.19 (1H, m), 2.30-1.25 (20H, m), 2.32 (2H, t, J J 6.8 Hz), 0.92 (3H, t, J = 7.0 Hz).

Reference example 13

(5Z,13E)-17,17-propano-16-t-butyldimethylsilyloxy-9-oxoprosta-5,10, 13-trenoic acid·methylester

[0160]



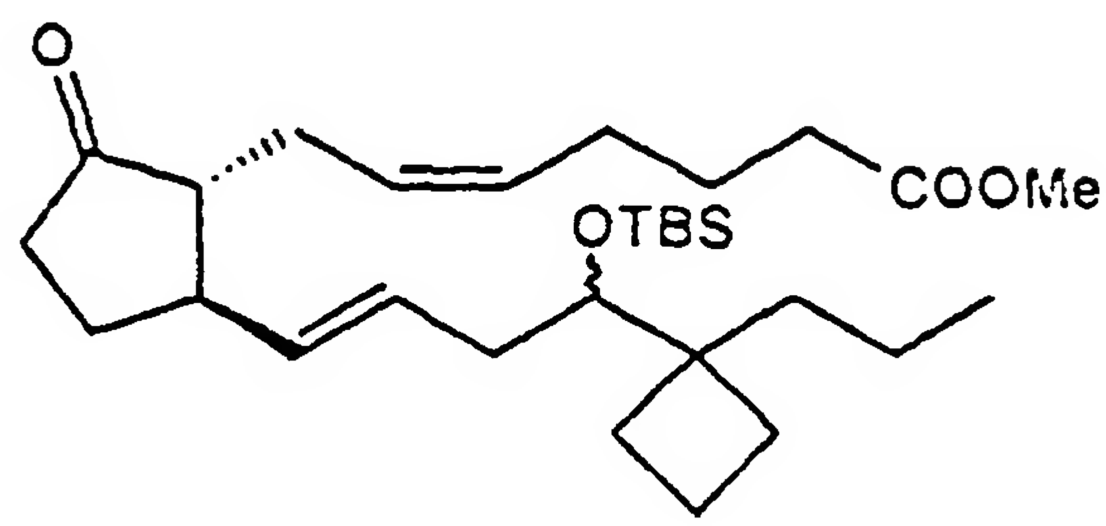
[0161] To a solution of the compound prepared in reference example 12 (60 mg) and 2,6-lutidine (116 µl) in anhydrous dichloromethane (5 ml) was added dropwise trifluoromethanesulfonic acid t-butyldimethylsilylester (190 µl) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium hydrogencarbonate, extracted with hexane (x2). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate) to give the title compound (44 mg) having the following physical data.

TLC: Rf 0.53 (hexane : ethyl acetate = 4 : 1).

Reference example 14

(5Z,13E)-17,17-propano-16-t-butyldimethylsilyloxy-9-oxoprosta-5,13-dienoic acid · methylester

[0162]



[0163] To a suspension of lithium aluminum hydride (48 mg) in anhydrous THF (1 ml) was added a suspension of copper iodide (I) (190 mg) in THF-HMPA (1 : 1, 2 ml) at -78 °C under an atmosphere of argon. The mixture was stirred at same temperature for 30 min. To the mixture was added dropwise a solution of the compound prepared in reference example 13 (43 mg) in anhydrous THF (2 ml). The reaction mixture was stirred at same temperature for 30 min. To the reaction mixture was added a saturated aqueous solution of sodium ammonium, warmed up at room temperature, filtered. The precipitate was washed with ether. The water layer of the filtrate was extracted with ether. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate) to give the title compound (25 mg) having the following physical data.

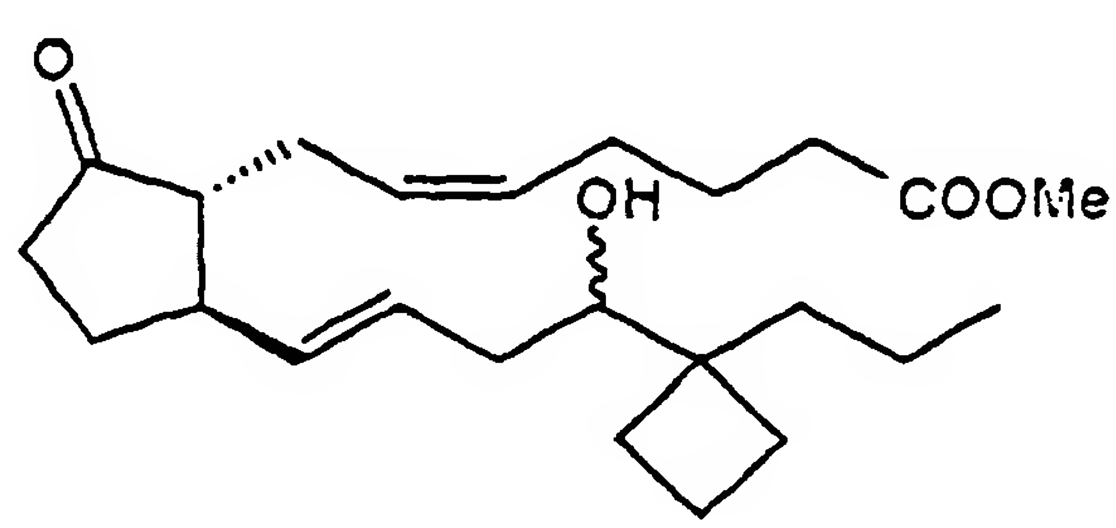
Rf 0.41 (hexane ethyl acetate = 4 : 1);

NMR ($CDCl_3$) : δ 5.60-5.25 (4H, m), 3.66 (3H, s), 3.57 (1H, m), 2.50. 1.20 (24H, m), 2.30 (2H, t, J = 6.8 Hz), 0.98-0.85 (12H, m), 0.03 (6H, s).

Example 7

(5Z,13E)-17,17-propano-16-hydroxy-9-oxoprosta-5,13-dienoic acid · methylester

[0164]



[0165] By the same procedure as provided in example 1, using the compound prepared in reference example 14, compounds of the present invention having the following physical data were obtained. less polar

TLC: Rf 0.81(hexane : ethyl acetate = 1 : 1);

NMR ($CDCl_3$) : δ 5.58-5.33 (4H, m), 3.67 (3H, s), 3.51 (1H, dd, j=10.2, 2.6 Hz), 2.56-1.24 (25H, m), 2.33 (2H, t, J=7.6 Hz), 0.94 (3H, t, J=7.0 Hz).

more polar

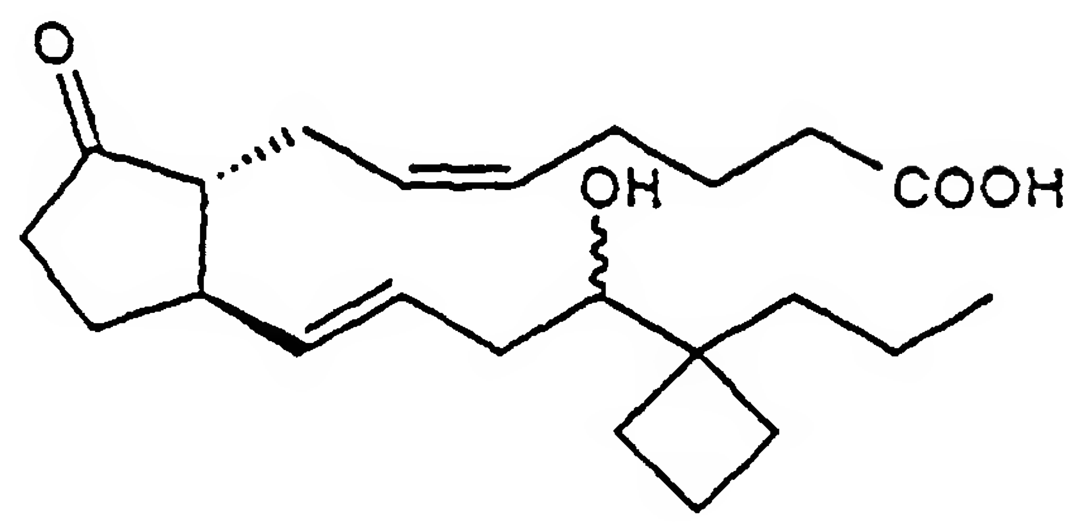
TLC: Rf 0.76(hexane : ethyl acetate = 1 : 1);

NMR($CDCl_3$) : δ 5.70-5.25 (4H, m), 3.67 (3H, s), 3.53 (1H, dd, J=10.0, 2.4 Hz), 2.58-1.22 (25H, m). 2.32 (2H, t, J=7.6 Hz), 0.94 (3H, t, J=6.8 Hz).

Example 8

(5Z,13E)-17,17-propano-16-hydroxy-9-oxoprosta-5,13-dienoic acid

[0166]



[0167] By the same procedure as provided in example 4, using the compound prepared in example 7, compounds of the present invention having the following physical data were obtained.

less polar

TLC: Rf 0.74 (hexane : ethyl acetate : acetic acid = 100 : 100 : 1);

NMR ($CDCl_3$) : δ 5.58-5.37 (4H, m), 5.40-3.40 (2H, br), 3.60 (1H, dd, J=10.2, 2.2 Hz), 2.53-1.20 (24H, m), 2.30 (2H, t, J=6.8 Hz), 0.93 (3H, t, J=6.8 Hz).

more polar

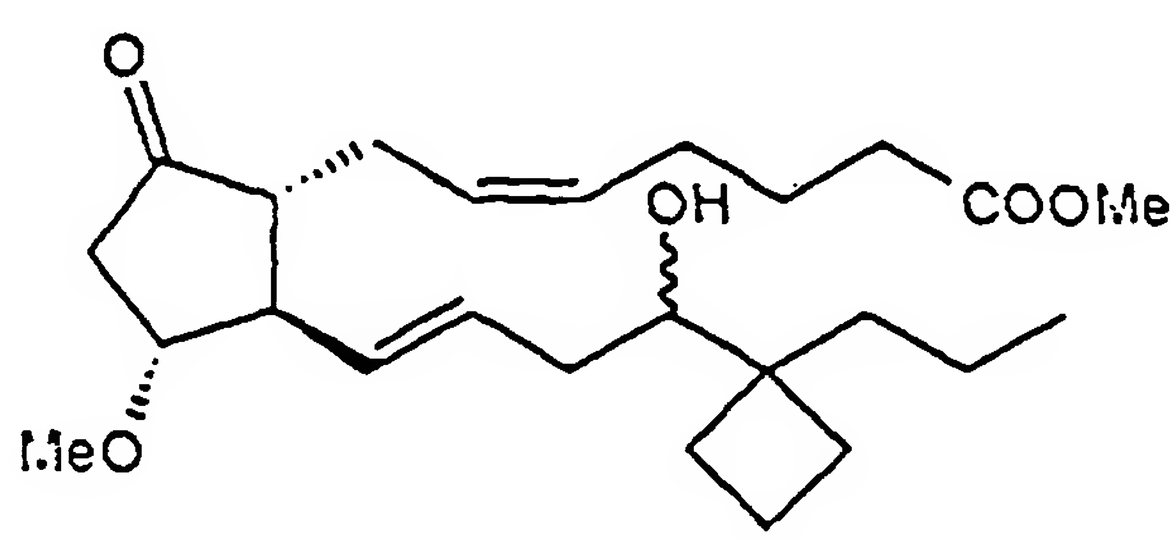
TLC: Rf 0.71 (hexane : ethyl acetate : acetic acid = 100 : 100 : 1);

NMR($CDCl_3$) : δ 5.62-5.37 (4H, m), 5.60-3.20 (2H, br), 3.64-3.53 (1H, m), 2.55-1.20 (24H, m), 2 30 (2H, t, J=6.8 Hz), 0.94 (3H, t, J=6.8 Hz).

Example 9

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13-dienoic acid · methylester

[0168]



[0169] To a solution of the compound prepared in example 1 (more polar; 78 mg) in ether (5 ml) was added silica gel (kiesel gel) (4.7 g). To the mixture was added dropwise a solution of diazomethane in ether under cooling with ice. The suspension was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (kiesel gel 7734, 20 g, hexane : ethyl acetate = 5 : 1 → 3 : 1) to give the present invention compound (more polar: 45 mg) having the following physical data.

more polar

Rf 0.57 (hexane : ethyl acetate = 1 : 1);

NMR ($CDCl_3$) : δ 5.67 (1H, ddd, J=15.4, 7.6, 5.8 Hz), 5.51 (1H, dd, J=15.4, 7.8 Hz), 5.50-5.26 (2H, m), 3.77-3.63 (1H, m), 3.67 (3H, s), 3.53 (1H, dd, J=10.2, 2.4 Hz), 3.37 (3H, s), 2.76 (1H, ddd, J=18.6, 7.2, 1.2 Hz), 2.54 (1H, dt, J=11.8, 7.8 Hz), 2.45-1.20 (21H, m), 2.31 (2H, t, J=7.5 Hz), 0.94 (3H, t, J=6.9 Hz).

[0170] By the same reaction as provided in above method, using the less polar compound prepared in example 1, compound (less polar: 47 mg) of the present invention having the following physical data was obtained.

less polar

Rf 0.66 (hexane : ethyl acetate = 1 : 1);

NMR ($CDCl_3$) : 5.74-5.26 (4H, m), 3.78-3.65 (1H, m), 3.67 (3H, s), 3.54 (1H, dd, J=10.0, 2.4 Hz), 3.38 (3H, s), 2.77 (1H, ddd, J=18.4, 7.0, 1.0 Hz), 2.55 (1H, d, J=11.6, 7.4 Hz), 2.40-1.20 (21H, m), 2.32 (2H, t, J=7.4 Hz), 0.94 (3H, t, J=6.9 Hz).

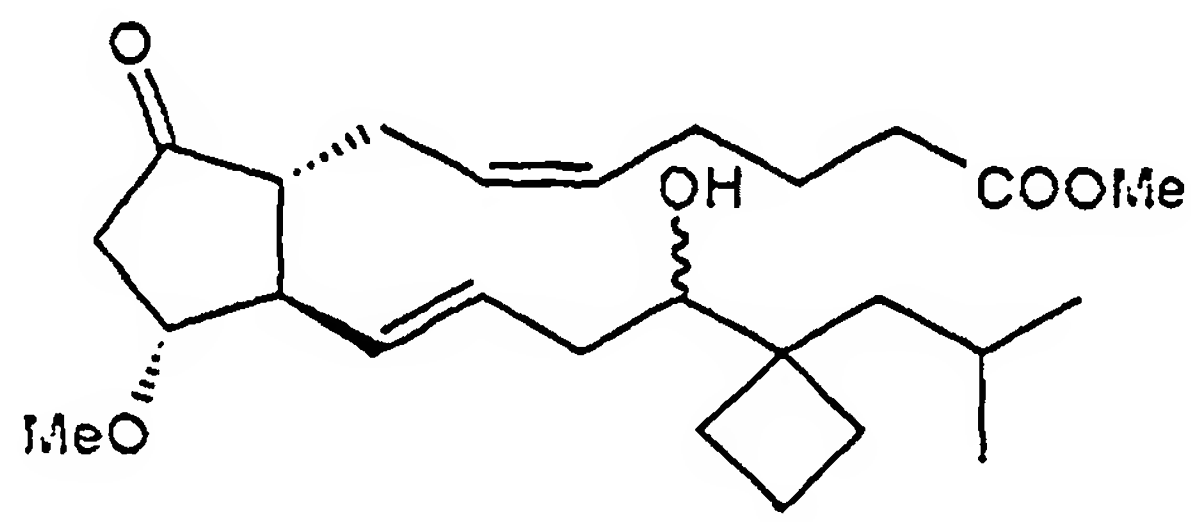
Example 9(1)~9(4)

[0171] By the same procedure as provided in example 9, compounds of the present invention having the following physical data were obtained.

Example 9(1)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-19-methylprosta-5,13-dienoic acid · methylester

[0172]



more polar

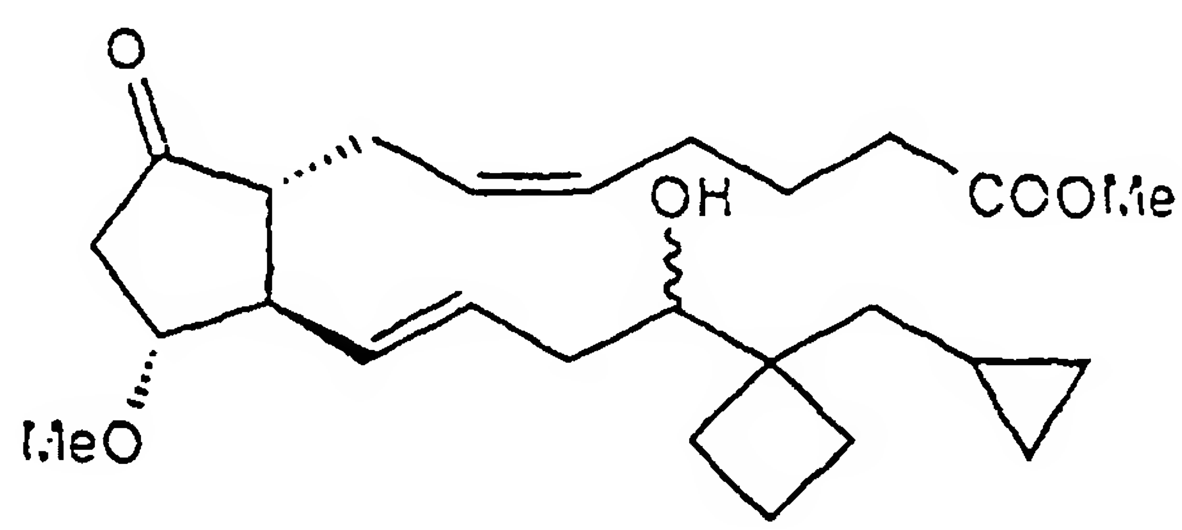
TLC: Rf 0.72 (hexane : ethyl acetate = 1:1);

NMR ($CDCl_3$): δ 5.79-5.25 (4H, m), 3.77-3.60 (2H, m), 3.66 (3H, S), 3.37 (3H, s), 2.76 (1H, ddd, J=18.4, 7.6, 1.2 Hz), 2.61-1.20 (21H, m), 2.33 (2H, t, J=6.9 Hz), 0.93 (3H, d, J=1.0 Hz), 0.90 (3H, d, J=1.0 Hz).

Example 9(2)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-19,20-methanoprosta-5,13-dienoic acid · methylester

[0173]



more polar

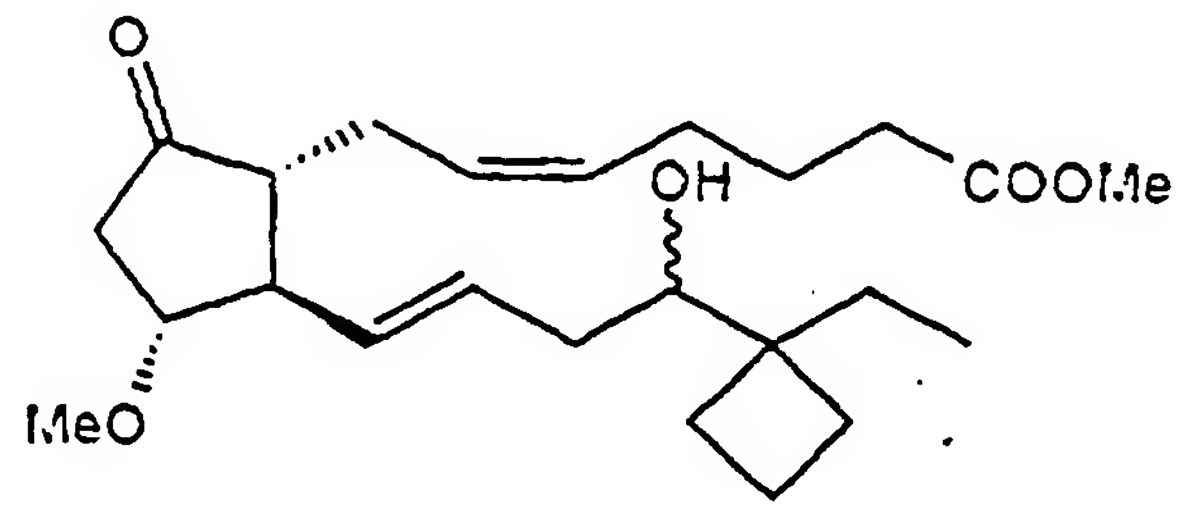
TLC: Rf 0.63 (hexane ethyl acetate = 1:1),

NMR ($CDCl_3$) : δ 5.77-5.23 (4H, m), 3.76-3.64 (2H, m), 3.66 (3H, S), 3.37 (3H, s), 2.76 (1H, ddd, J=18.4, 7.0, 1.2 Hz), 2.61-1.23 (20H, m), 2.33 (2H, t, J=6.9 Hz), 0.90-0.70 (1H, m), 0.55-0.45 (2H, m), 0.15-0.05 (2H, m).

Example 9(3)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-20-norprosta-5,13-dienoic acid · methylester

[0174]



more polar

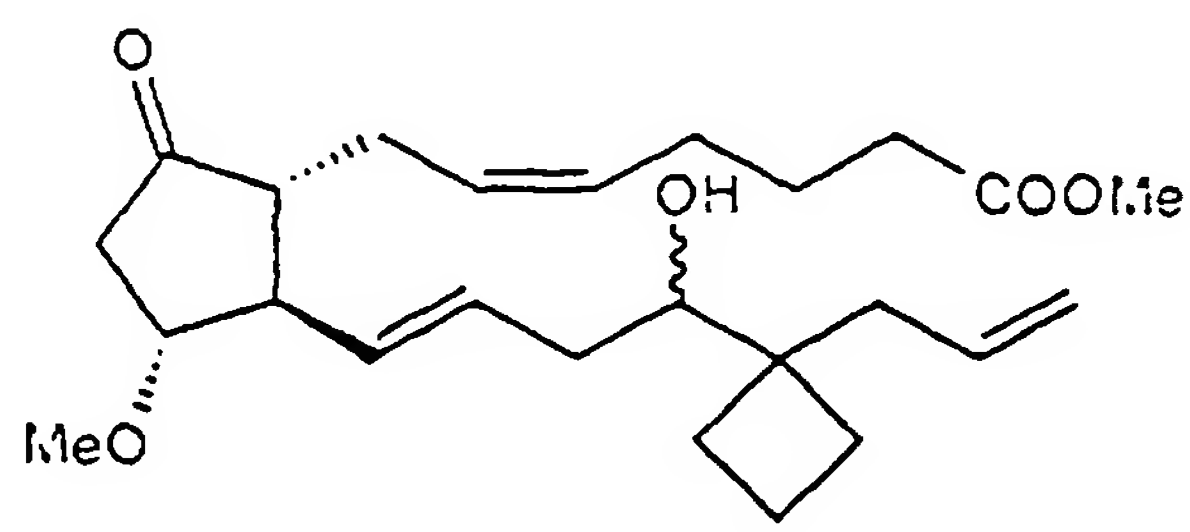
TLC: Rf 0.56 (hexane : ethyl acetate = 1:1);

NMR ($CDCl_3$): δ 5.75-5.27 (4H, m), 3.76-3.64 (1H, m), 3.66 (3H, s), 3.54 (1H, dd, J=10.0, 2.4 Hz), 3.37 (3H, s), 2.76 (1H, ddd, J=18.4, 7.0, 1.2 Hz), 2.60-1.35 (20H, m), 2.31 (2H, t, J=6.8 Hz), 0.92 (3H, t, J=7.2 Hz).

Example 9(4)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13,19-trienoic acid · methylester

[0175]



more polar

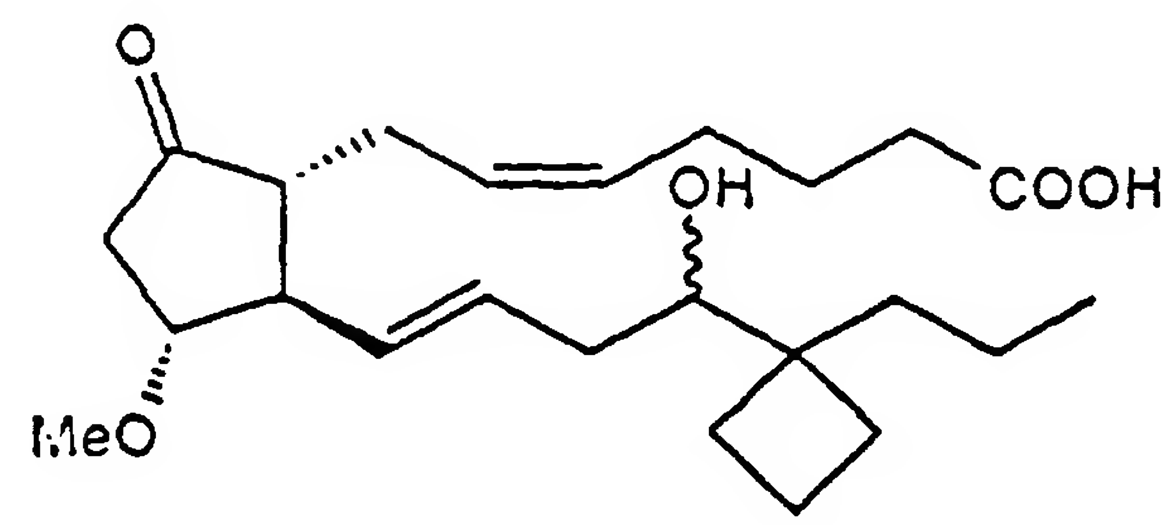
TLC: Rf 0.53 (hexane : ethyl acetate = 1:1);

NMR ($CDCl_3$): δ 6.03-5.81 (1H, m), 5.75-5.23 (4H, m), 5.15-5.06 (2H, m), 3.76-3.64 (1H, m), 3.54 (1H, dd, J=10.4, 2.2 Hz), 3.37 (3H, s), 2.76 (1H, ddd, J=18.4, 7.0, 1.4 Hz). 2.60-1.50 (20H, m), 2.31 (2H, t, J=6.9 Hz).

Example 10

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13-dienoic acid

[0176]



[0177] By the same procedure as provided in example 4, using the compound prepared in example 9 (less polar or more polar), compounds of the present invention having the following physical data were obtained.

less polar

TLC: Rf 0.40 (hexane ethyl acetate : methanol = 1 : 1 : 0.02);

NMR ($CDCl_3$) : δ 5.66 (1H, ddd, J=15.4, 7.6, 5.4 Hz), 5.50 (1H, dd, J=15.4, 7.2 Hz), 5.50-5.30 (2H, m), 4.50-2.50 (2H, br), 3.78-3.63 (1H, m), 3.63 (1H, dd, J=10.4, 2.4 Hz), 3.38 (3H, s), 2.77 (1H, ddd, J=18.2, 7.0, 1.0 Hz), 2.51 (1H, ct, J=11.4,7.8 Hz), 2.40-1.20, 20H, m), 2.34 (2H, t, J=6.8 Hz, 0.94 (3H, t, J=6.7 Hz).

TLC Rf 0.36 (hexane : ethyl acetate : methanol = 1 : 1 : 0.02).

NMR ($CDCl_3$) : δ 5.69 (1H, ddd, J=15.4, 6.6, 6.0 Hz), 5.54 (1H, dd, J=15.4, 7.2 Hz), 5.50-5.30 (2H, m), 5.00-3.00 (2H, br), 3.77-3.63 (1H, m), 3.60 (1H, dd, J=10.0, 2.4 Hz), 3.37 (3H, s), 2.77 (1H, ddd, J=18.2, 7.2, 1.2 Hz), 2.53 (1H, dt, J=11.2, 7.8 Hz), 2.42-1.20 (20H, m), 2.34 (2H, t, J=7.1 Hz), 0.94 (3H, t, J=6.8 Hz).

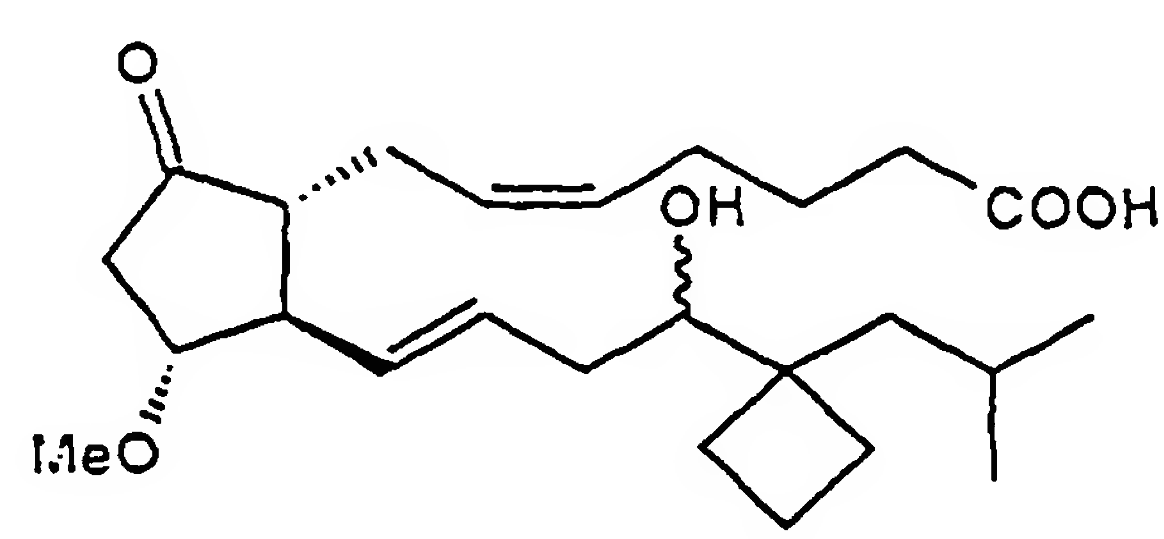
Example 10(1)~10(4)

[0178] By the same procedure as provided in example 10, compounds of the present invention having the following physical data were obtained.

Example 10(1)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-19-methyl-9-oxoprosta-5,13-dienoic acid

[0179]



more polar

TLC: Rf 0.28 (hexane : ethyl acetate = 1:1);

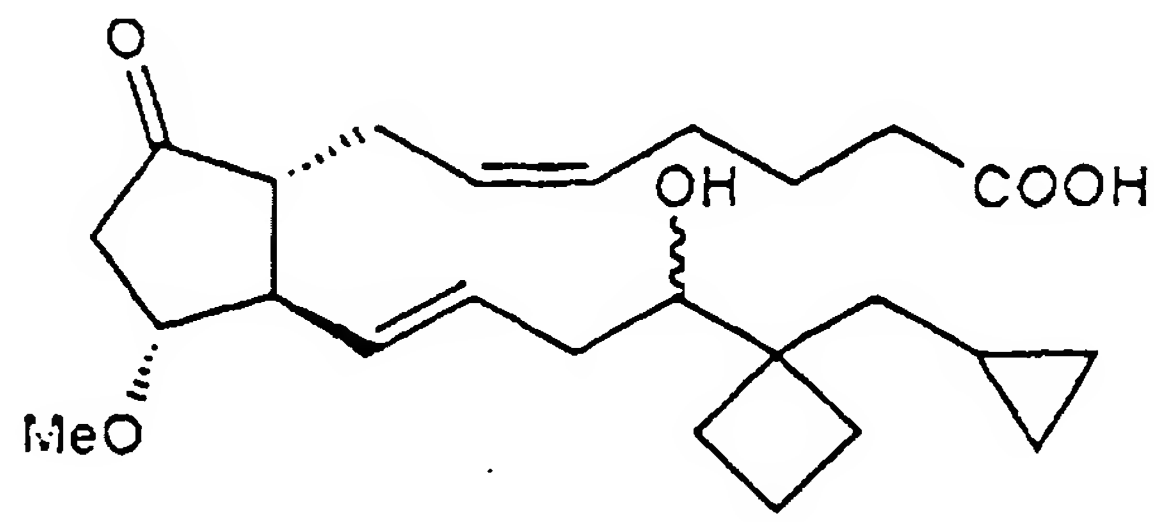
NMR ($CDCl_3$): δ 5.78-5.28 (4H, m), 5.00-4.00 (2H, br), 3.77-3.64 (2H, m), 3.37 (3H, s), 2.77 (1H, dd, J=18.4, 7.4

Hz), 2.60-1.22 (20H, m), 2.34 (2H, t, J=6.9 Hz), 0.93 (3H, d, J=1 2 Hz), 0.90 (3H, d, J=1.0 Hz).

Example 10(2)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-19,20-methanoprosta-5,13-dienoic acid

[0180]



more polar

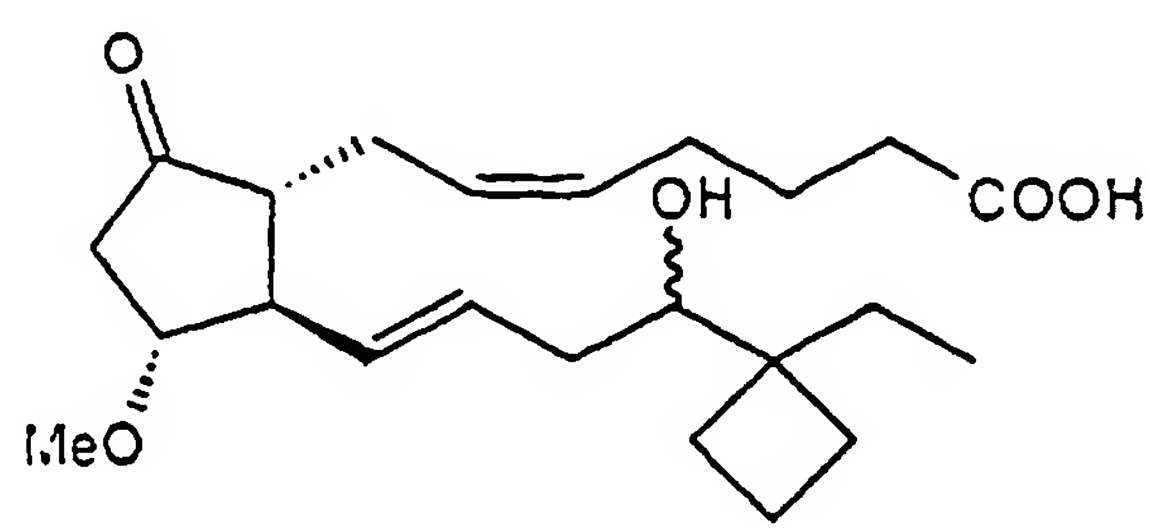
TLC: Rf 0.29 (hexane : ethyl acetate = 1:1);

NMR ($CDCl_3$): δ 5.80-5.30 (4H, m), 3.79-3.64 (2H, m), 3.38 (3H, s), 2.77 (1H, dd, J=18.2, 7.2 Hz), 2.59-1.10 (23H, m). 0.95-0.70 (1H, m), 0.55-0.45 (2H, m), 0.15-0.05 (2H, m).

Example 10(3)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-20-norprosta-5,13-dienoic acid

[0181]



more polar

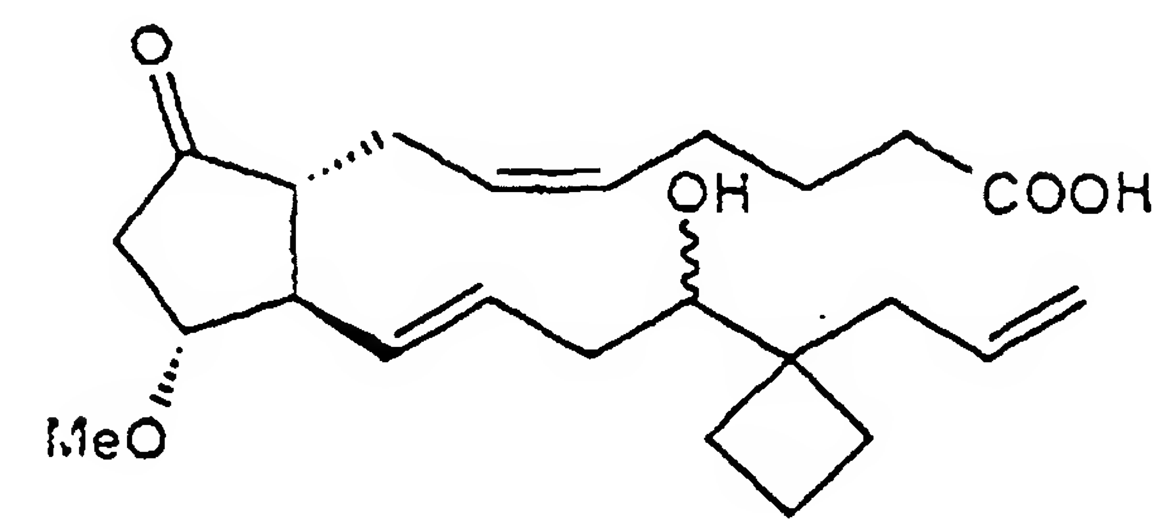
TLC: Rf 0.27 (hexane : ethyl acetate = 1:1);

NMR ($CDCl_3$): δ 5.78-5.30 (4H, m), 3.76-3.58 (2H, m), 3.60-2.60 (2H, br), 3.37 (3H, s), 2.77 (1H, ddd, J=18.4, 7.0, 1.4 Hz), 2.60-1.32 (19H, m), 2.33 (2H, t, J=7.0 Hz), 0.92 (3H, t, J=7.4 Hz).

Example 10(4)

(5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13,19-trienoic acid

[0182]



more polar

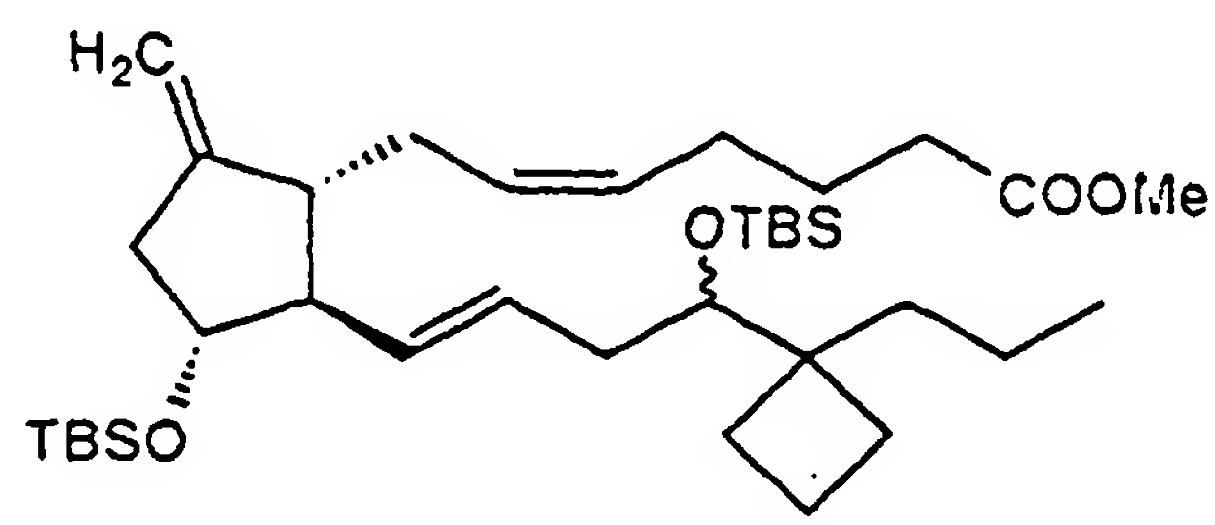
TLC: Rf 0.25 (hexane : ethyl acetate = 1:1);

NMR ($CDCl_3$): δ 6.03-5.82 (1H, m), 5.77-5.30 (4H, m), 5.17-5.07 (2H, m), 4.40-1.40 (2H, br), 3.76-3.59 (2H, m), 3.37 (3H, s), 2.77 (1H, ddd, J=18.4, 7,2, 1.2 Hz), 2.59-1.60 (19H, m), 2.33 (2H, t, J=7.0 Hz).

Reference example 15

(5Z,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9,9-methyleneprosta-5,13-dienoic acid · methylester

[0183]



[0184] To a stirred suspension of zinc powder (2.875 g) in THF (25 ml) was added dropwise dibromomethane (1.01 ml) at room temperature under an atmosphere of argon. After the reaction mixture cooled at -40 °C, to the mixture was slowly added dropwise titanium tetrachloride (1.13 ml). The mixture was stirred at 5 °C for 3 days, Nozaki-Lombardo reagent was obtained as a grayish suspension.

[0185] To a stirred solution of the compound prepared in reference example 3 (150 mg) in dichloromethane (3 ml) was added the above obtained Nozaki-Lombardo reagent (3 ml) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was quenched by addition of ice and a saturated aqueous solution of sodium hydrogencarbonate, extracted with ether (x3). The extract was washed with water (x2), a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck Kiesel gel 7734, 20 ml, ethyl acetate : hexane = 1 : 40) to give the title compound (120 mg) as a colorless oil having the following physical data.

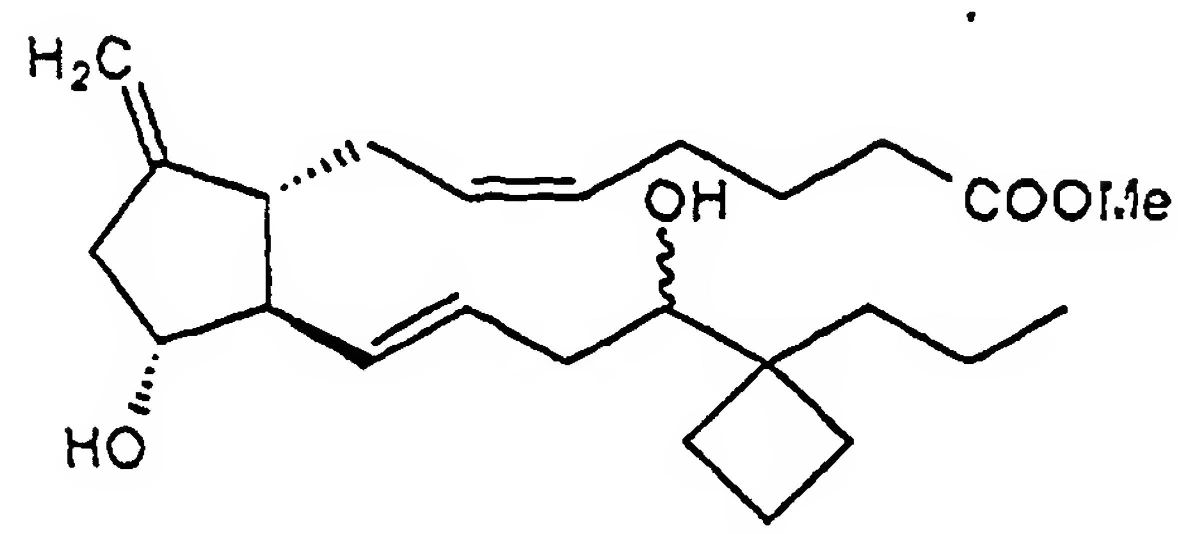
TLC: Rf 0.47 (ethyl acetats : hexane = 1 : 20);

NMR ($CDCl_3$) : δ 5.65-5.15 (4H, m), 4.68 (1H, brs), 4.83 (1H, brs), 3.77 (1H, q, J = 7.5 Hz), 3.66 (3H, S), 3.55 (1H, t, J = 5.0 Hz), 2.60 (1H, dd, J = 16.5, 7.0 Hz), 2.40-1.15 (23H, m), 0.90 (9H, s), 0.87 (9H, s), 1.00-0.80 (3H, m), 0.05 (6H, s), 0.02 (6H, s).

Example 11

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9,9-methyleneprosta-5,13-dienoic acid · methylester

[0186]



[0187] By the same procedure as provided in example 1, using the compound prepared in reference example 15, compounds of the present invention having the following physical data were obtained.
less polar

TLC: Rf 0.39 (ethyl acetate : hexane = 1 : 2);

NMR ($CDCl_3$) : δ 5.70-5.30 (4H, m), 4.96 (1H, brs), 4.88 (1H, brs), 3.83 (1H, q, J=7.5 Hz), 3.67 (3H, s), 3.52 (1H, dd, J=10.0, 2.0 Hz), 2.76 (1H, dd, J=16.0, 7.0 Hz), 2.40-1.20 (25H, m), 0.93 (3H, t, J=7.0 Hz).

more polar

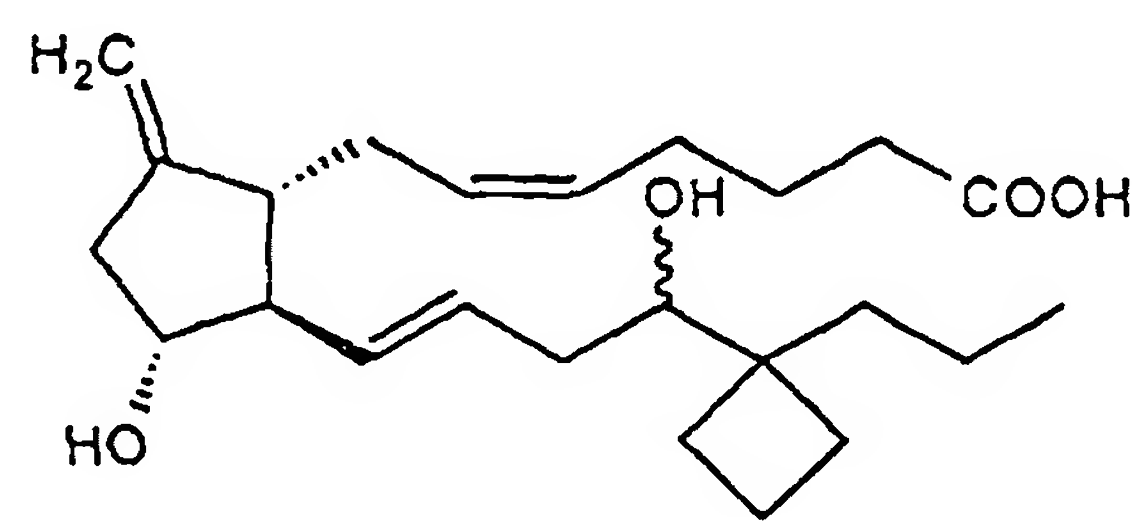
TLC: Rf 0.33 (ethyl acetate : hexane = 1:2);

NMR ($CDCl_3$): δ 5.70-5.30 (4H, m), 4.95 (1H, brs), 4.88 (1H, brs), 3.82 (1H, c J=7.0 Hz), 3.70 (3H, s), 3.53 (1H, dd, J=10.0, 2.5 Hz), 2.75 (1H, dd, J=16.0, 7.0 Hz), 2.40-1.20 (25H, m), 0.94 (3H, t, J=7.0 Hz).

Example 12

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9,9-methyleneprosta-5,13-dienoic acid

[0188]



[0189] By the same procedure as provided in example 4, using the compound prepared in example 11, compounds of the present invention having the following physical data were obtained.
less polar

TLC: Rf 0.52 (ethyl acetate : hexane : acetic acid = 9 : 10 : 1);

NMR($CDCl_3$) : δ 5.70-5.30 (4H, m), 4.96 (1H, brs), 4.89 (1H, brs), 3.82 (1H, q, J=8.5 Hz), 3.61 (1H, dd, J=10, 2.5 Hz), 2.74 (1H, dd, J=15.5, 7.0 Hz), 2.40-1.20 (25H, m), 0.93 (3H, t, J=7,0 Hz).

more polar

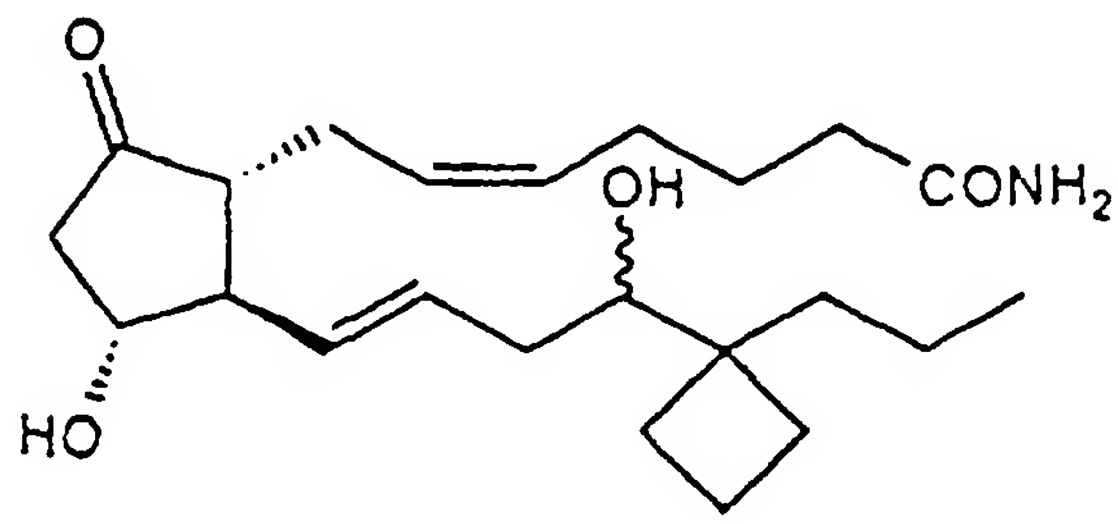
TLC: Rf 0.52 (ethyl acetate : hexane : acetic acid = 9:10:1);

NMR($CDCl_3$): δ 5.70-5.20 (4H, m), 4.95 (1H, brs), 4.88 (1H, brs), 3.81 (1H, q, J=6.5 Hz), 3.59 (1H, dd, J=10, 2.5 Hz), 2.73 (1H, dd, J=16.0, 7.0 Hz), 2.40-1.20 (25H, m), 0.94 (3H, t, J=7.0 Hz).

Example 13

(5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid amide

[0190]



[0191] To a stirred solution of the compound prepared in example 4 (less polar; 42 mg) in dichloromethane (1 ml) was added triethylamine (81 ml) and isobutyl chloroformate (60 ml) at 0 °C. After the mixture was stirred for 30 min, to the mixture was added ammonia in water solution (0.5 ml). The reaction mixture was stirred for 10 min. The reaction mixture was quenched by addition of 1N aqueous solution of hydrochloric acid, extracted with ethyl acetate (x3). The extract was washed with water (x2), 1N aqueous solution of hydrochloric acid (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purged by column chromatography on silica gel (Merck Kiesel gel 7734, 5 ml, ethyl acetate : hexane = 3 : 2 → MeOH : $CHCl_3$ = 1 : 19 → 1 : 9) to give the present invention compound (32 mg) as a pale yellow oil having the following physical data.
less polar

TLC: Rf 0.52 (methanol : chloroform = 1 : 9);

NMR ($CDCl_3$): δ 5.90-5.20 (6H, m), 4.10 (1H, q, J=9.0 Hz), 3.55 (1H, d, J=8.0 Hz), 2.73 (1H, dd, J=11.0, 7.5 Hz), 2.75-2.55 (1H, m), 2.55-1.20 (24H, m), 0.94 (3H, t, J=6.5 Hz).

[0192] By the same procedure as provided in above example, using the compound prepared in example 4 (more polar), compound of the present invention having the following physical data was obtained.
more polar

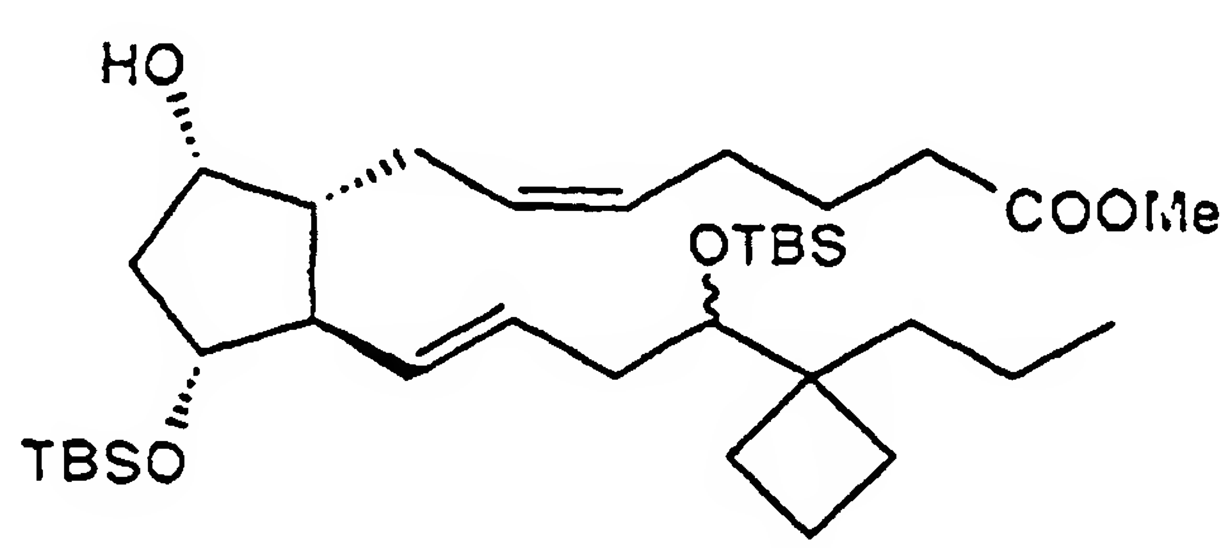
TLC: Rf 0.52 (methanol : chloroform = 1 : 9);

NMR ($CDCl_3$): δ 5.90-5.60 (2H, m), 5.60-5.20 (4H, m), 4.07 (1H, q, J=8.5 Hz), 3.55 (1H, dd, J=10.0, 2.0 Hz), 3.04 (1H, brs), 2.74 (1H, ddd, J=18.0, 7.0, 1.0 Hz), 2.75-2.50 (1H, m), 2.50-1.20 (23H, m), 0.94 (3H, t, J=7.0 Hz).

Reference example 16

(5Z,9α,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-hydroxyprosta-5,13-dienoic acid · methylester

[0193]



[0194] To a solution of (5Z,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-oxoprosta-5,13-dienoic acid · methylester (740 mg, the compound prepared in reference example 3) in THF (20 ml) was added dropwise L-S electride (1.76 ml; 1.0 M in THF solution) at -78 °C under an atmosphere of argon. After the mixture was stirred at

same temperature for 30 min, to the solution was added dropwise a 30% aqueous solution of hydroperoxide (1 ml) at same temperature. The reaction mixture was warmed up to 0 °C. The reaction mixture was quenched by addition of 2N aqueous solution of hydrochloric acid (1 ml), extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck Kiesel gel 7734, 30 g, hexane ethyl acetate = 9.1) to give the tittle compound (558 mg) as a pale yellow oil having the following physical data.

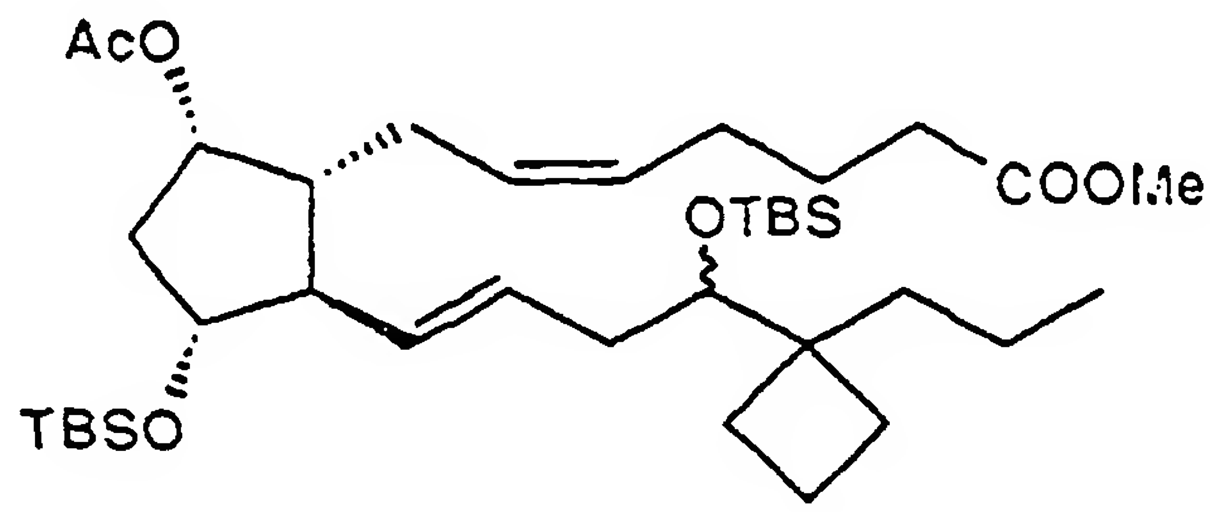
TLC: Rf 0.35 (hexane ethyl : acetate = 9:1);

NMR ($CDCl_3$) : δ 5.60-5.10 (4H, m), 4.15-3.90 (2H, m), 366 (3H, s), 3.55 (1H, t, J=5 Hz), 2.70-2.50 (1H, m), 2.40-1.20 (24H, m), 1.00-0.80 (21H, m), 0.10-0.00 (12H, m).

Reference example 17

(5Z,9α,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-acetyloxy-prosta-5,13-dienoic acid · methylester

[0195]



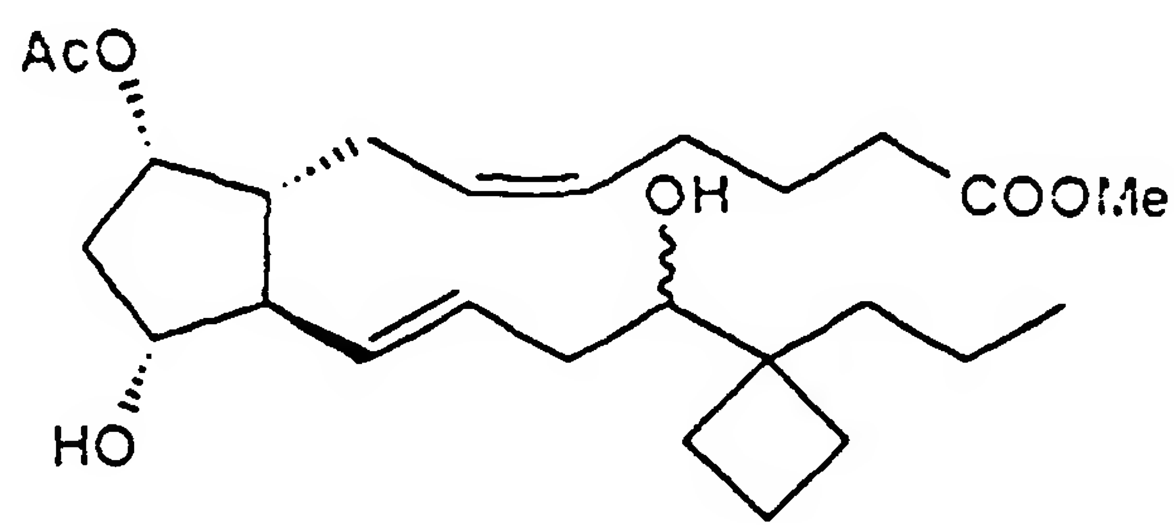
[0196] To a solution of the compound prepared in reference example 16 (518 mg) in pyridine (1 ml) was added acetic anhydride (0.15 ml) and dimethylaminopyridine (catalytic amount). The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched by addition of water, extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, water and a saturated aqueous solution of sodium chloride, succssively, dried, filered, and concentrated to give the title compound having the following physical data.

TLC: Rf 0.42 (hexane : ethyl acetate = 9 : 1).

Reference example 18

(5Z,9α,11α,13E)-17,17-propane-11,16-dihydroxy-9-acetyloxy-prosta-5,13-dienoic acid · methylester

[0197]



[0198] To a solution of the compound prepared in reference example 17 in acetonitrile (10 ml) was added dropwise 48% aqueous solution of hydrofluoric acid (0.5 ml) under cooling with ice. The reaction mixture was stirred at room temperature for 1.5 hours. The react on mixture was quenched by addition of a saturated aqueous solution of sodium hydrogencarbonate, extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by Lobar column chromatography (size B, hexane : ethyl

acetate = 2 : 3) to aive the title two compounds (less polar; 142 mg, more polar; 148 mg) having the following physical data.
less polar

TLC: Rf 0.30 (hexane : ethyl acetate = 1 : 1);

NMR ($CDCl_3$) : δ 5.66 (1H, ddd. J=15.0, 7.8, 5.0 Hz), 5.45-5.30 (3H, m), 5.15-5.05 (1H, m), 4.00-3.85 (1H, m), 3.67 (3H, s), 3.55 (1H, dd, J=10.0, 2.4 Hz), 2.55-2.40 (1H, m), 2.40-1.30 (23H, m), 2.31 (2H, t, J=7.4 Hz), 2.06 (3H, s), 0.94 (3H, t, J=7.2 Hz). more polar

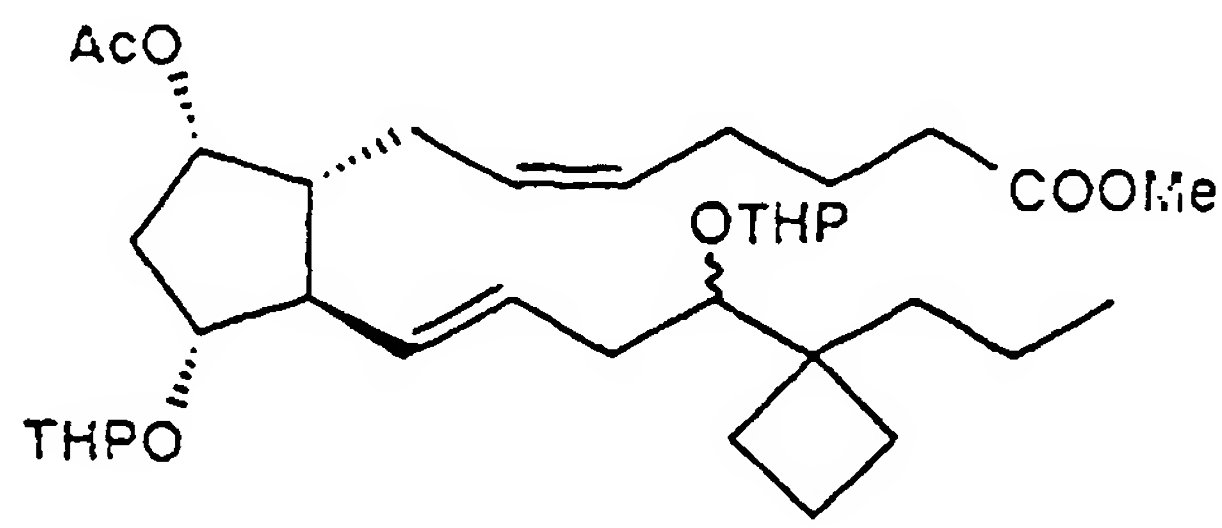
TLC: Rf 0.23 (hexane : ethyl acetate = 1 : 1);

NMR($CDCl_3$) : δ 5.65 (1H, ddd, J=14.8, 8.0, 6.2 Hz), 5.43-5.25 (3H, m), 5.15-5.05 (1H, m), 3.95-3.82 (1H, m), 3.67 (3H, s), 3.55 (1H, dd, J=10.0, 2.4 Hz), 2.60-2.40 (1H, m), 2.40-1.20 (23H, m), 2.30 (2H, t, J=7.4 Hz), 2.06 (3H, s), 0.94 (3H, t, J=6.7 Hz).

Reference example 19

(5Z,9α,11α,13E)-17,17-propano-11,16-bis(2-tetrahydropyranyloxy)-9-acetyloxy-prosta-5,13-denoic acid·methylester

[0199]



[0200] To a stirred solution of the compound prepared in reference example 18 (less polar; 64 mg) in dichloromethane (1 ml) was added dihydropyran (400 ml) and PPTS (pyridinium p-toluenesulfonate; 4 mg) at room temperature under an atmosphere of argon. The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched by addition of water and a saturated aqueous soluton of sodium hydrogencarbonate, extracted with ethyl acetate (x3). The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Fuji Silysia BW-300 20 ml, ethyl acetate : hexane = 1 : 7 → 1 : 5) to give the title compound (77.5 mg) as a colorless oil having the following physical data.

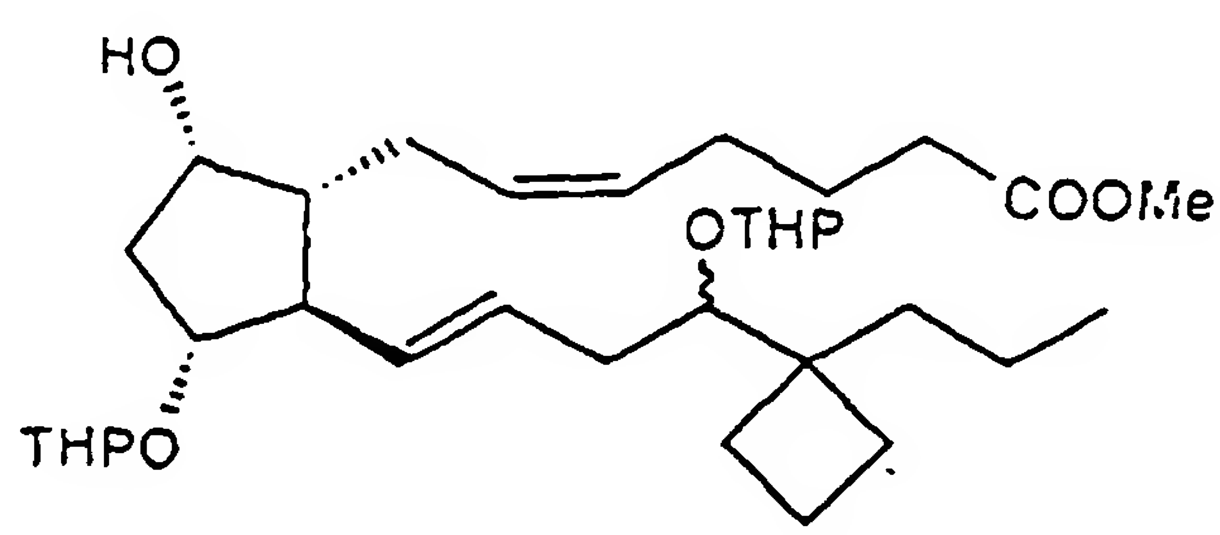
TLC: Rf 0.37 (ethyl acetate : hexane = 1 : 4);

NMR ($CDCl_3$) : δ 5.85-5.45 (1H, m), 5.45-5.20 (3H, m), 5,10-4.98 (1H, m), 4.75-4.55 (2H, m), 4.05-3.70 (3H, m), 3.67 (3H, s), 3.65-3.38 (3H, m), 2.60-1.20 (36H, m), 2.04 (3H, s), 1.00-0.85 (3H, m).

Reference example 20

(5Z,9α,11α,13E)-17,17-propano-11,16-bis(2-tetrahydropyranyloxy)-9-hydroxyprosta-5,13-dienoic acid · methylester

[0201]



[0202] To a stirred solution of the compound prepared in reference example 19 (77 mg) in methanol (2 ml) was added potassium carbonate (15 mg) at room temperature under an atmosphere of argon. The reaction mixture was stirred at room temperature for 1 day. The reaction mixture was quenched by addition of water and 1N aqueous solution of hydrochloric acid, extracted with ethyl acetate (x3). The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734, 20 ml, ethyl acetate : hexane = 1 : 4 → 1 : 3) to give the title compound (70 mg) as a colorless oil having the following physical data.

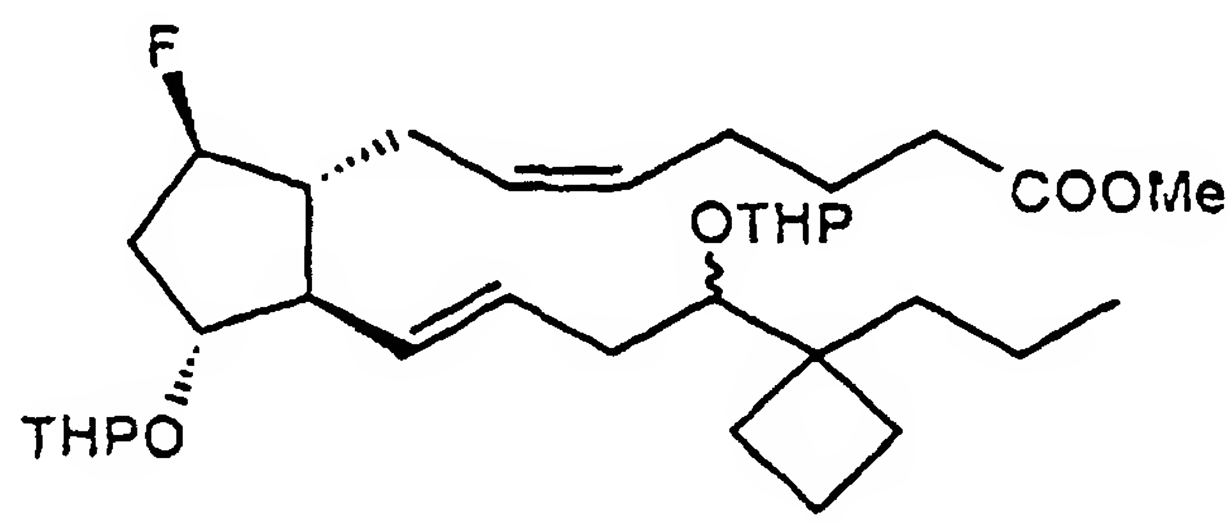
TLC: Rf 0.39 (ethyl acetate : hexane = 1 : 2);

NMR ($CDCl_3$) : δ 5.75 (4H, m), 4.75-4.55 (2H, m), 4.20-3.75 (4H, m), 3.67 (3H, s), 3.62-3.38 (3H, m), 2.60-1.20 (34 H, m), 2.32 (2H, t, J = 7.5 Hz), 0.93 (3H, 1, J = 7.5 Hz).

Reference example 21

(5Z,9β,11α,13E)-17,17-propano-11,16-bis(2-tetrahydropyranyloxy)-9-fluoroprosta-5,13-dienoic acid · methylester

[0203]



[0204] To a stirred solution of the compound prepared in reference example 20 (70 mg) in dichloromethane (2 ml) was added DAST (20 ml, diethylaminosulfur trifluoride) at -78 °C under an atmosphere of argon. The reaction mixture was stirred for 20 min. The reaction mixture was quenched by addition of water and a saturated aqueous solution of sodium hydrogencarbonate, extracted with ethyl acetate (x3). The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Fuji Silysia BW-300 20 ml, ethyl acetate : hexane = 1 : 10) to give the title compound (36 mg) as a colorless oil having the following physical data.

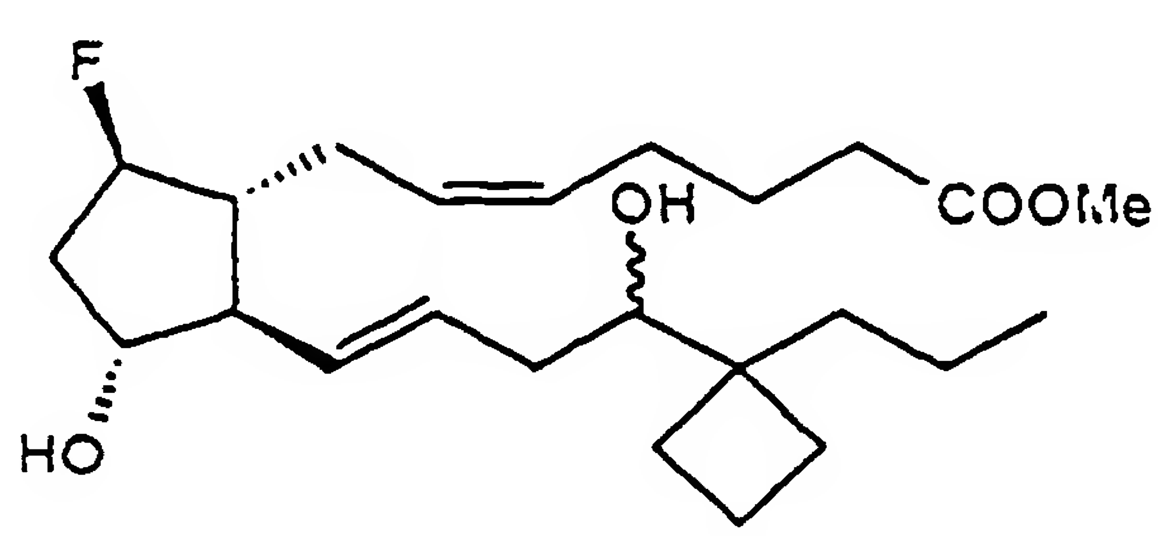
TLC: Rf 0.46 (ethyl acetate : hexane = 1 : 5);

NMR ($CDCl_3$) : δ 5.90-5.20 (4H, m), 4.75-4.55 (2H, m), 4.40-3.75 (3H, m), 3.67 (3H, s), 3.67-3.40 (3H, m), 2.60-1.20 (35H, m), 2,32 (2H, t, J = 7.5 Hz), 0.93 (3H, t, J = 6.5 Hz).

Example 14

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-fluoro-prosta-5,13-dienoic acid · methylester

[0205]



[0206] To a stirred mixture of the compound prepared in reference example 21 (36 mg) in THF (1 ml) and water (0.5 ml) was added acetic acid (2 ml) at room temperature. The reaction mixture was stirred at 45 °C. The reaction mixture was quenched by addition of water, extracted with ethyl acetate (x3). The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734, 20 ml, ethyl acetate : hexane = 1 : 2 → 1 : 1) and (Merck Lobar prepackaged column size A, ethyl acetate : hexane = 2 : 1) to give the present invention compound (12 mg) having the following physical data.
less polar

TLC: Rf 0.54 (ethyl acetate : hexane = 1 : 1);

NMR ($CDCl_3$): δ 5.80-5.40 (4H, m), 4.95-4.55 (1H, m), 4.20-4.00 (1H, m), 3.67 (3H, s), 3.54 (1H, dd, J=10.0, 2.5 Hz), 2.40-1.20 (24H, m), 2.33 (2H, t, J=7.5 Hz), 0.94 (3H, t, J=7.0 Hz).

[0207] By the same procedure as provided in reference example 19, 20 21 and example 14, using the compound prepared in reference example 18 (more polar), compound of the present invention having the following physical data was obtained. more polar

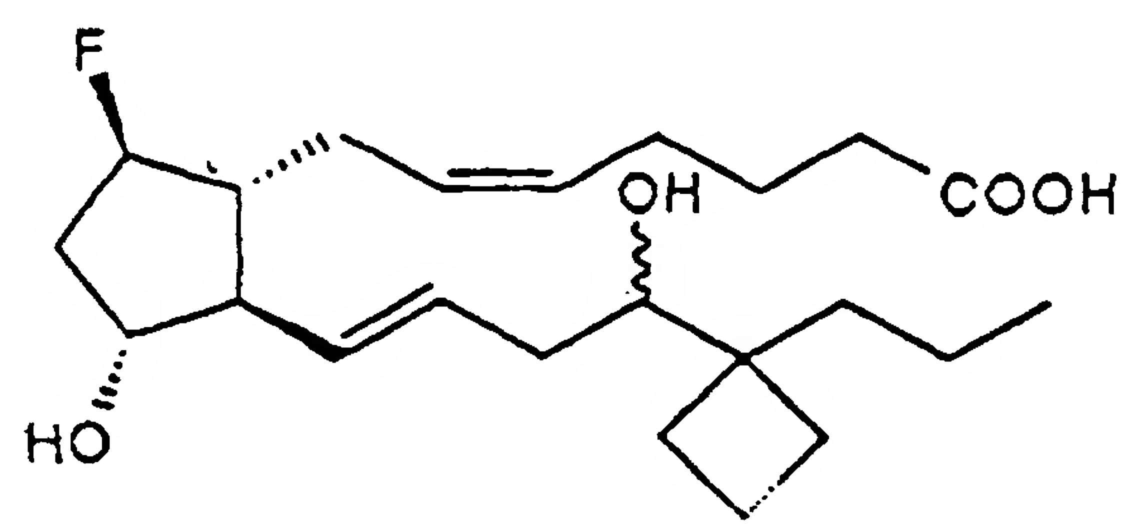
TLC: Rf 0.48 (ethyl acetate : hexane = 1:1);

NMR ($CDCl_3$): δ 5.80-5.30 (4H, m), 4.95-4.55 (1H, m), 4.20-4.00 (1H, m), 3.67 (3H, s), 3.53 (1H, dd, J=10.0, 2.0 Hz), 3.00-1.20 (24H, m), 2.32 (2H, t, J=7.5 Hz), 0.94 (3H, t, J=6.5 Hz).

Example 15

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-fluoro-prosta-5,13-dienoic acid

[0208]



[0209] To a stirred solution of the compound prepared in example 14 (10 mg) in methanol (1 ml) was added 2N aqueous solution of sodium hydroxide (0.3 ml) at room temperature under an atmosphere of argon. The reaction mixture was stirred for 2 hours. The reaction mixture was quenched by addition of water and 1N aqueous solution of hydrochlorie acid, extracted with ethyl acetate (x3). The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated to give the present invention compound (10 mg) as a colorless oil having the following physical data.
less polar

TLC: Rf 0.38 (ethyl acetate : hexane = 3:1);

NMR ($CDCl_3$): δ 5.80-5.30 (4H, m), 5.00-4.60 (1H, m), 4.20-4.00 (1H, m), 3.62 (1H, dd, J=10.0, 2.0 Hz), 2.34 (2H, t, J=6.5 Hz), 2.40-1.20 (24H, m), 0.94 (3H, t, J=6 5 Hz).

[0210] By the same procedure as provided in example 15, using the compound prepared in example 14 (more polar), compound of the present invention having the following physical data was obtained.
more polar

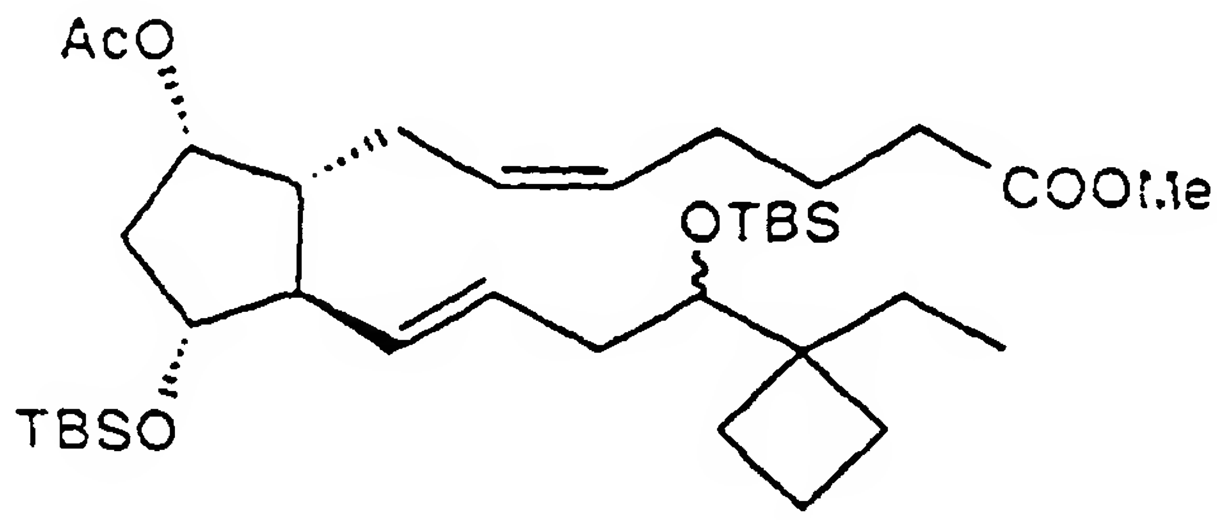
TLC: Rf 0.35 (ethyl acetate : hexane = 3:1);

NMR ($CDCl_3$): δ 5.80-5.30 (4H, m), 5.00-4.80 (1H, m), 4.20-4.00 (1H, m), 3.59 (1H, d, J=10.5 Hz), 2.35 (2H, t, J=7.0 Hz), 2.40-1.20 (24H, m), 0.94 (3H, t, J=6.5 Hz).

Reference example 22

(5Z,9α,11α,13E)-17,17-propane-11,16-bis(t-butyldimethylsilyloxy)-9-acetyloxy-20-norprosta-5,13-dienoic acid · methylester

[0211]



[0212] To a stirred solution of (5Z,9α,11α,13E)-17,17-propano-11,16-dihydroxy-9-acetyloxy-20-norprosta-5,13-dienoic acid · methylester (119 mg; more polar the compound prepared in same method by reference example 18) in dichloromethane (2 ml) was added 2,6-lutidine (0.26 ml) and trifluoromethanesulfonic acid t-butyldimethylsilylester (0.26 ml) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched by addition of water, extracted with ethyl acetate (x3). The extract was washed with 0.1 N aqueous solution of hydrochloric acid (x2), water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated to give the tittle compound (211 mg) as a colorless oil having the following physical data.

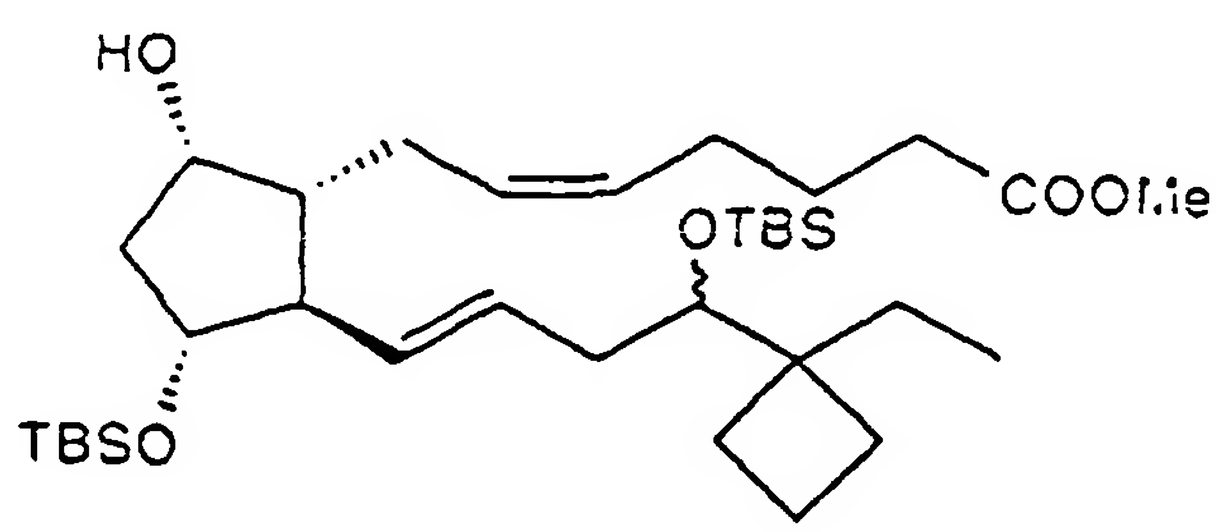
TLC: Rf 0.45 (ethyl acetate : hexane = 1 : 8);

NMR ($CDCl_3$) : δ 5.70-5.45 (1H, m), 5.32 (1H, t, J = 4.5 Hz), 5.25-5.05 (1H, m), 5.05-4.95 (1H, m), 3.90-3.70 (1H, m), 3.6 (3H, s), 358 (1H, t, J = 5.0 Hz), 2.50-1.35 (21H, m), 2.29 (2H, t, J = 7.5 Hz), 2.04 (3H, s), 1.00-0.80 (3H, m), 0.91 (9H, s), 0.85 (9H, s), 0.06 (3H, s), 0.05 (3H, s), 0.01 (6H, s).

Reference example 23

(5Z,9α,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-hydroxy-20-norprosta-5,13-dienoic acid methylester

[0213]



[0214] To a stirred solution of the compound prepared in reference example 22 (211 mg) in methanol (3 ml) was added potassium carbonate (60 mg) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 1 day. The reaction mixture was quenched by addition of water and 1N aqueous solution of hydrochloric acid, extracted with ethyl acetate (x3). The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734, 20 ml, ethyl acetate : hexane = 1 : 8) to give the title compound (161 mg) as a colorless oil having the following physical data.

TLC: Rf 0.35 (ethyl acetate : hexane = 1 : 8);

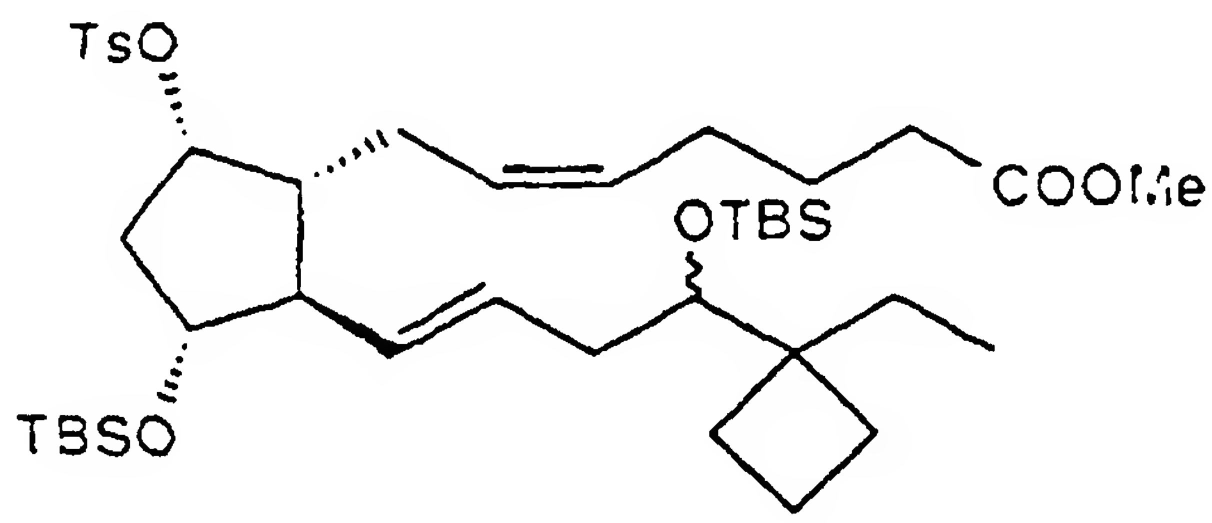
NMR ($CDCl_3$) : δ 5.60-5.15 (4H, m), 4.20-4.00 (1H, m), 4.00-3.95 (1H, m), 3.66 (3H, s), 3.57 (1H, t, J = 5.0 Hz),

2.61 (1H, d, J = 9.0 Hz), 2.42-1.35 (20H, m), 2.31 (2H, t, J = 7.5 Hz), 1.00-0.80 (3H, m), 0.90 (9H, s), 0.87 (9H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (6H, s).

Reference example 24

(5Z,9α,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-tosyloxy-20-norprosta-5,13-dienoic acid · methylester

[0215]



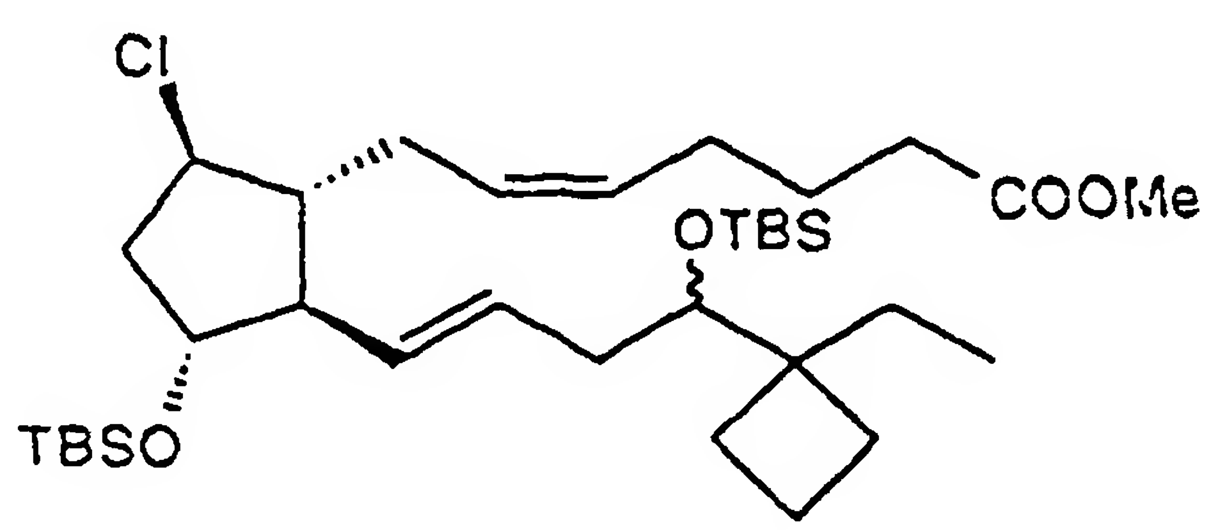
[0216] To a stirred solution of the compound prepared in reference example 23 (161 mg) in pyridine (1 ml) was added tosyl chloride (102 mg) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at room temperature for 9 hours, the reaction mixture was quenched by addition of water, extracted with ethyl acetate (x3). The extract was washed with a saturated aqueous solution of sodium hydrogecarbonate (x2), water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated to give the title compound (194 mg) having the following physical data.

TLC: Rf 0.64 (ethyl acetate : hexane = 1 : 19).

Reference example 25

(5Z,9β,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-chloro-20-norprosta-5,13-dienoic acid · methylester

[0217]



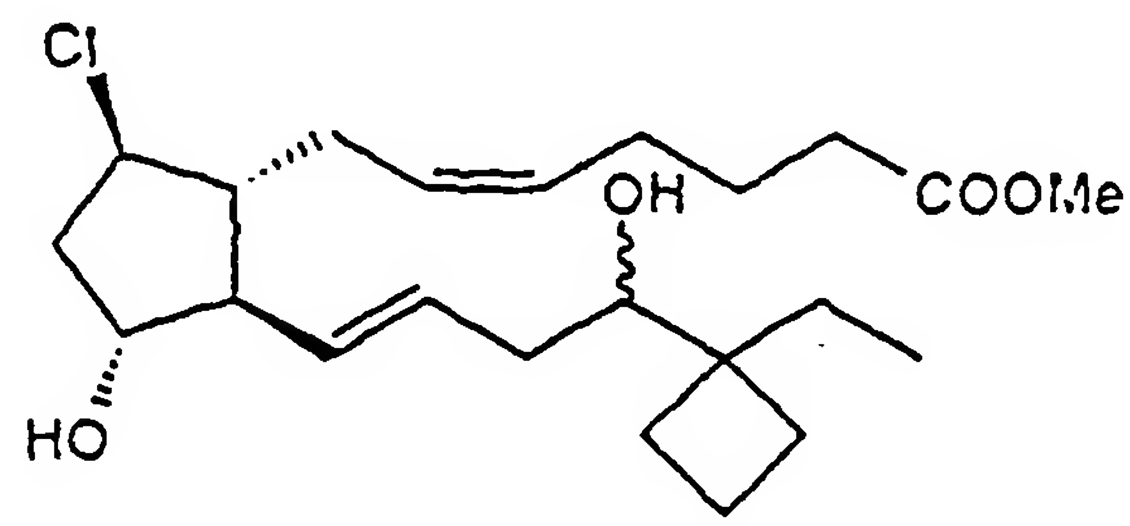
[0218] To a stirred solution of tetrabutylammonium chloride (742 mg) was added dropwise a solution of the compound prepared in reference example 24 (194 mg) in toluene (4 ml) under an atmosphere of argon. The reaction mixture was stirred at 40 °C for 12 hours. The reaction solution was changed to white suspension. The reaction mixture was quenched by addition of water, extracted with ethyl acetate (x3). The extract was washed with water (x2), a saturated aqueous solution of sodium hydrogencarbonate (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated to give the title compound (95 mg) having the following physical data.

TLC: Rf 0.67 (ethyl acetate : hexane = 1 : 8).

Example 16

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-20-norprosta-5,13-dienoic acid · methylester

[0219]



[0220] By the same procedure as provided in example 14, using the compound prepared in reference example 25, compound of the present invention having the following physical data was obtained.
more polar

TLC: Rf 0.49 (ethyl acetate hexane = 1:1);

NMR ($CDCl_3$): δ 5.60 (1H, ddd, J=15, 8, 6 Hz), 5.50-5.33 (3H, m), 4.20-3.95 (2H, m), 3.67 (3H, s), 3.53 (1H, dd, J=10.5, 2.5 Hz), 2.32 (2H, t, J=7.0 Hz), 2.40-1.50 (21H, m), 1.45 (1H, sept, J=7.0 Hz), 0.91 (3H, t, J=7.5 Hz).

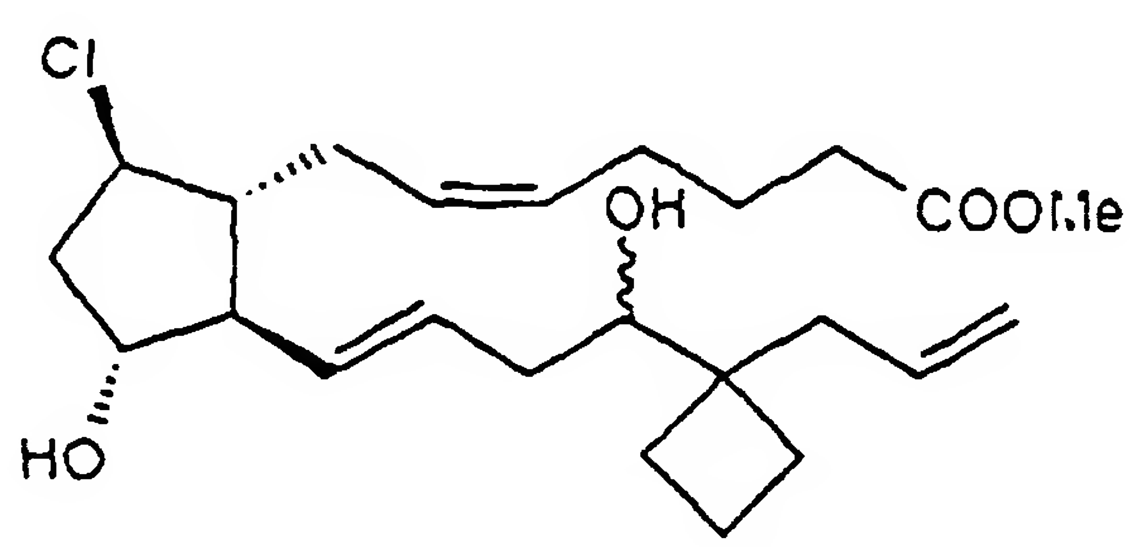
Example 16(1)~16(6)

[0221] By the same procedure as provided in example 16, using the compound prepared in reference example 22, 23, 24, 25 or example 16, compounds of the present invention having the following physical data were obtained.

Example 16(1)

(5Z,9β,11α13E)-17,17-propane-11,16-d-hydroxy-9-chloroprosta-5,13,19-trienoic acid · methylester

[0222]



more polar

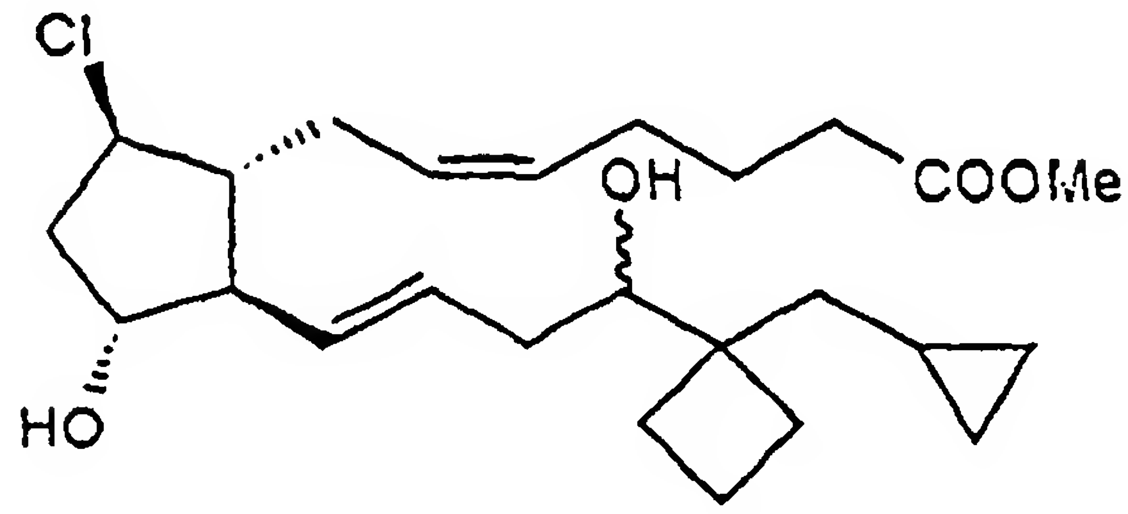
TLC: Rf 0.49 (ethyl acetate : hexane = 1:1);

NMR ($CDCl_3$): δ 6.06-5.83 (1H, m), 5.67-5.23 (4H, m), 5.20-5.04 (2H, m), 4.20-3.95 (2H, m), 3.67 (3H, s), 3.53 (1H, dd, J=10.0, 2.5 Hz), 2.60-1.50 (22H, m), 2.32 (2H, t, J=8.0 Hz).

Example 16(2)

(5Z,9β,11α,13E)-17,17-propano-19, 20-methano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid · methylester

[0223]



more polar

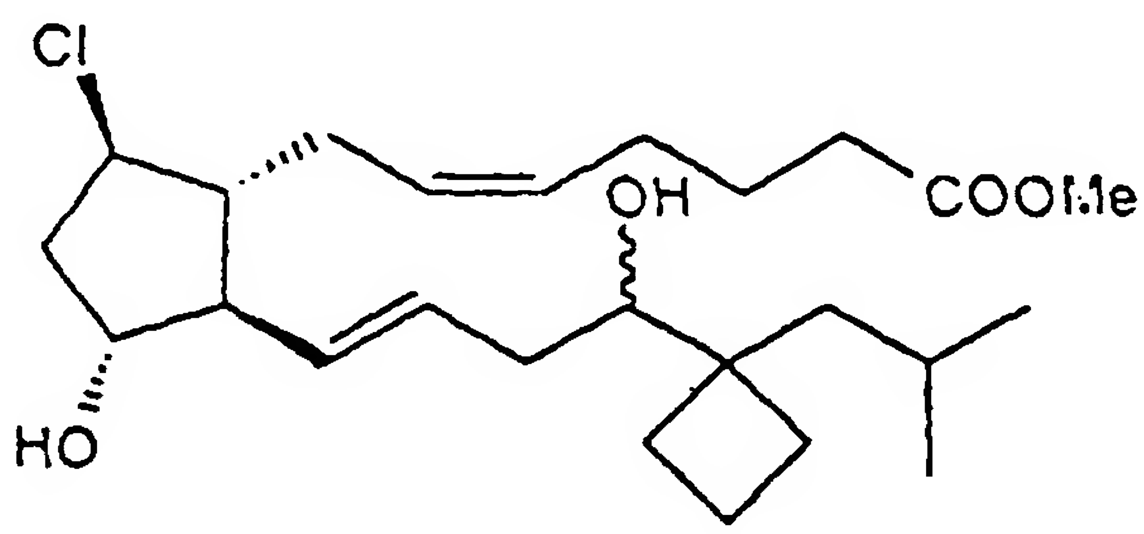
TLC: Rf 0.25 (hexane : ethyl acetate = 2:1);

NMR ($CDCl_3$): δ 5.61 (1H, ddd, J=15.4, 7.8, 5.4 Hz), 5.52-5.35 (3H, m), 4.18-3.94 (2H, m), 3.67 (3H, s), 3.67 (1H, dd, J=10.0, 2.2 Hz), 2.40-1.60 (20H, m), 2.33 (2H, t, J=7.4 Hz), 1.52 (1H, dd, J=14.4, 6.6 Hz), 1.35 (1H, dz, J=14.4, 6.2 Hz), 0.90-0.68 (1H, m), 0.55-0.45 (2H, m), 0.15-0.05 (2H, m).

Example 16(3)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19-methylprosta-5,13-dienoic acid · methylester

[0224]



more polar

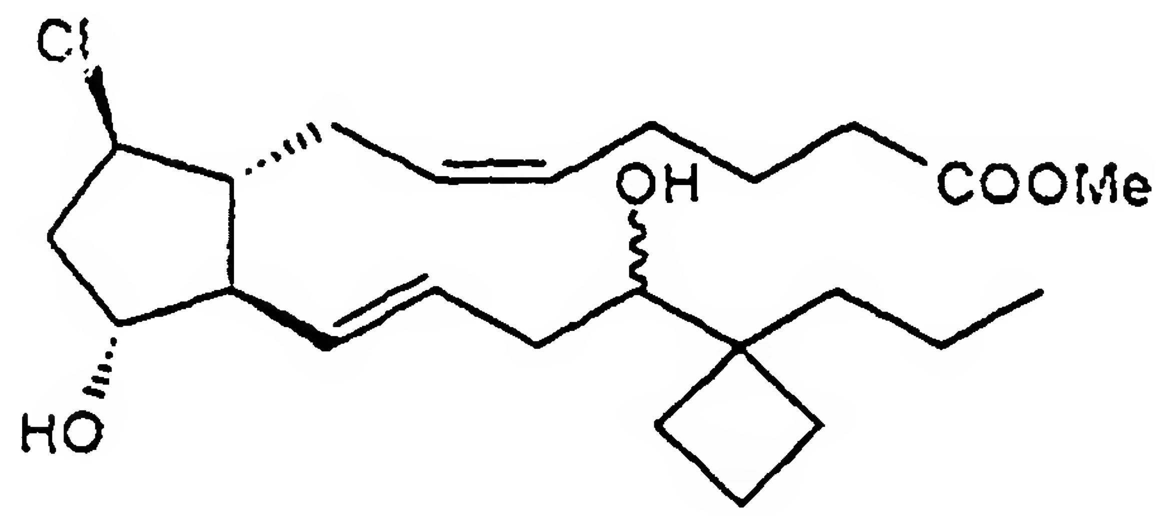
TLC: Rf 0.32 (hexane : ethyl acetate = 2:1);

NMR ($CDCl_3$): δ 5.62 (1H, ddd, J=15.4, 7.8, 5.4 Hz), 5.52-5.35 (3H, m), 4.18-3.94 (2H, m), 3.67 (3H, s), 3.61 (1H, dd, J=10.4, 2.2 Hz), 2.40-1.60 (21H, m), 2.33 (2H, t J=7.4 Hz), 1.55 (1H, dd, J=14.2, 66 Hz), 1.33 (1H, dd, J=14.2, 6.5 Hz), 0.918 (3H, d, J=6.6 Hz), 0.915 (3H, d, J=6.6 Hz).

Example 16(4)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid · methylester

[0225]



less polar

TLC: Rf 0.29 (hexane : ethyl acetate = 2:1),

NMR ($CDCl_3$): δ 5.61 (1H, ddd, J=15.4, 7.6, 5.8 Hz), 5.55-5.35 (3H, m), 4.20-3.95 (2H, m), 3.68 (3H, s), 3.53 (1H, dd, J=9.8, 2.2 Hz), 2.40-1.20 (24H, m), 2.33 (2H, t, J=7.6 Hz), 0.94 (3H, t, J=6.8 Hz).

more polar

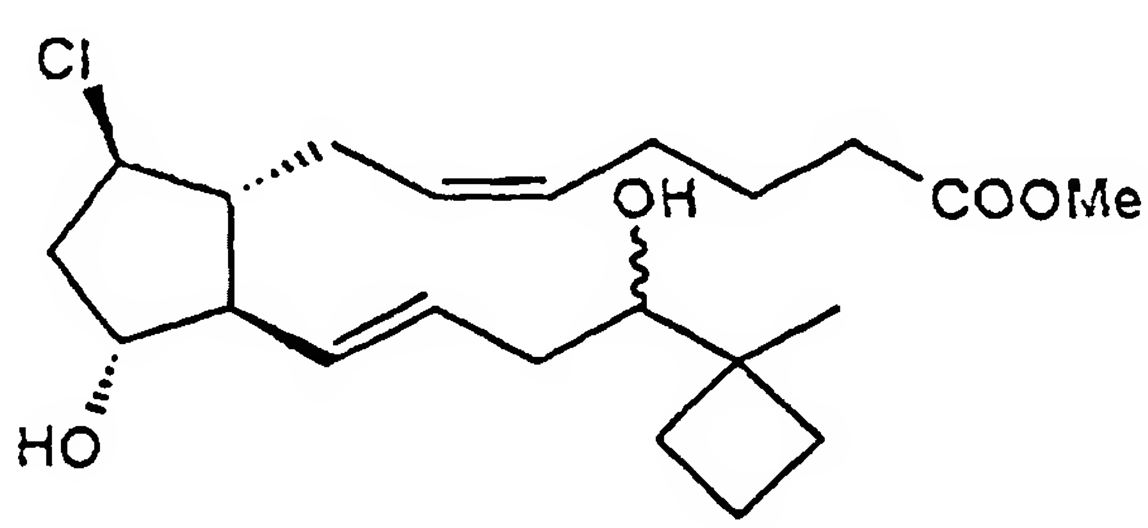
TLC: Rf 0.26 (hexane : ethyl acetate = 2:1);

NMR ($CDCl_3$) : δ 5.58 (1H, ddd, J=15.0, 8.2, 5.6 Hz), 5.50-5.32 (3H, m), 4.18-3.95 (2H, m), 3.67 (3H, s), 3.53 (1H, dd, J=10.4, 2.2 Hz), 2.76 (1H, br), 2.40-1.20 (23H, m), 2.33 (2H, t, J=7.3 Hz), 0.94 (3H, t, J=6.8 Hz).

Example 16(5)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19,20-dinorprosta-5,13-dienoic acid · methylester

[0226]



more polar

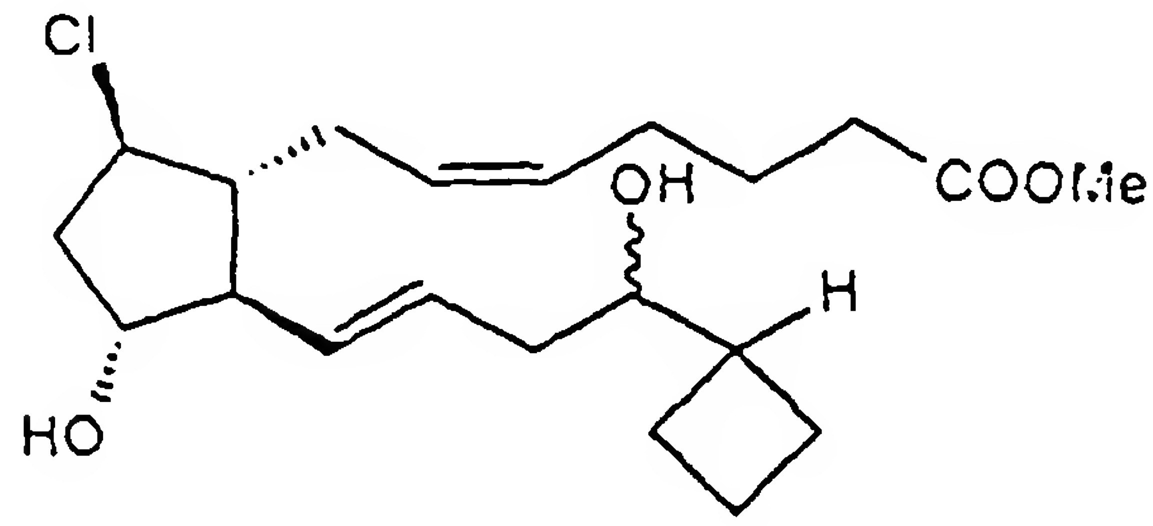
TLC: Rf 0.30 (hexane : ethyl acetate = 1 : 1);

NMR ($CDCl_3$) : δ 5.59 (1H, ddd, J=15, 8, 6Hz), 5.47-5.30 (3H, m), 4.18-3.95 (2H, m), 3.67 (3H, s), 3.53 (1H, dd, J=10, 2Hz), 2.40-1.55 (22H, m), 1.14 (2H, s).

Example 16(6)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-18,19,20-trinorprosta-5,13-dienoic acid · methylester

[0227]



more polar

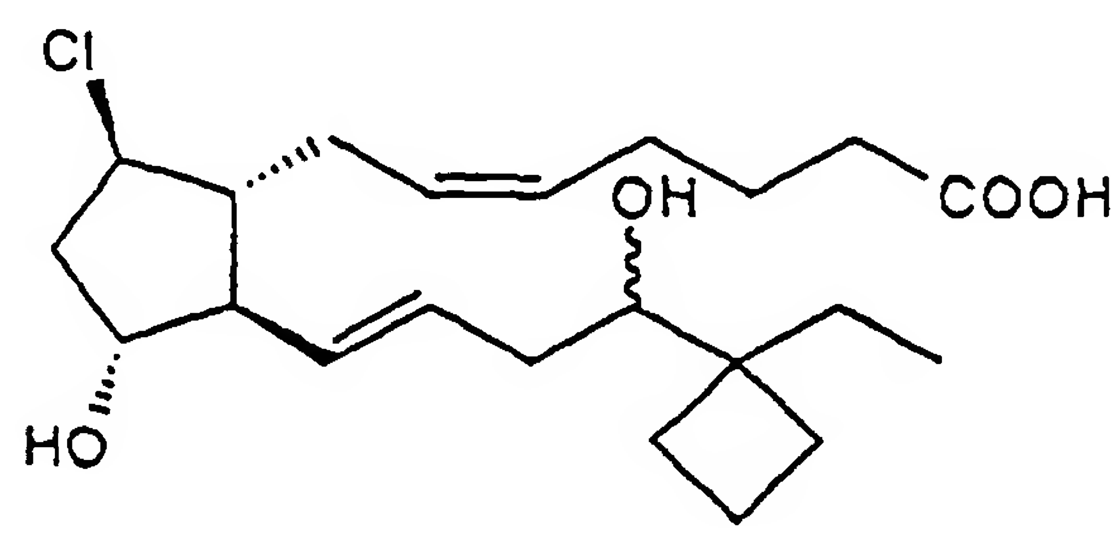
TLC: Rf 0.26 (hexane : ethyl acetate = 1 : 1);

NMR($CDCl_3$) : δ 5.60 (1H, ddd, J=15, 8, 6Hz), 5.49-5.31 (3H, m), 4.19-3.95 (2H, m), 3.67 (3H, s), 3.62-3.48 (1H, m), 2.60-1.60 (23H, m).

Example 17

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-20-norprosta-5,13-dienoic acid

[0228]



[0229] By the same procedure as provided in example 15, using the compound prepared in example 16, compound of the present invention having the following physical data was obtained.
more polar

TLC: Rf 0.44 (ethyl acetate : hexane : acetic acid = 6:3:0.1);

NMR ($CDCl_3$): δ 5.80-5.35 (4H, m), 4.20-4.00 (2H, m), 3.59 (1H, dd, J=10.5, 2.5 Hz), 2.36 (2H, t, J=7.0 Hz), 2.40-1.60 (19H, m), 1.45 (1H, sept, J=7.5 Hz), 0.92 (3H, t, J=7.5 Hz).

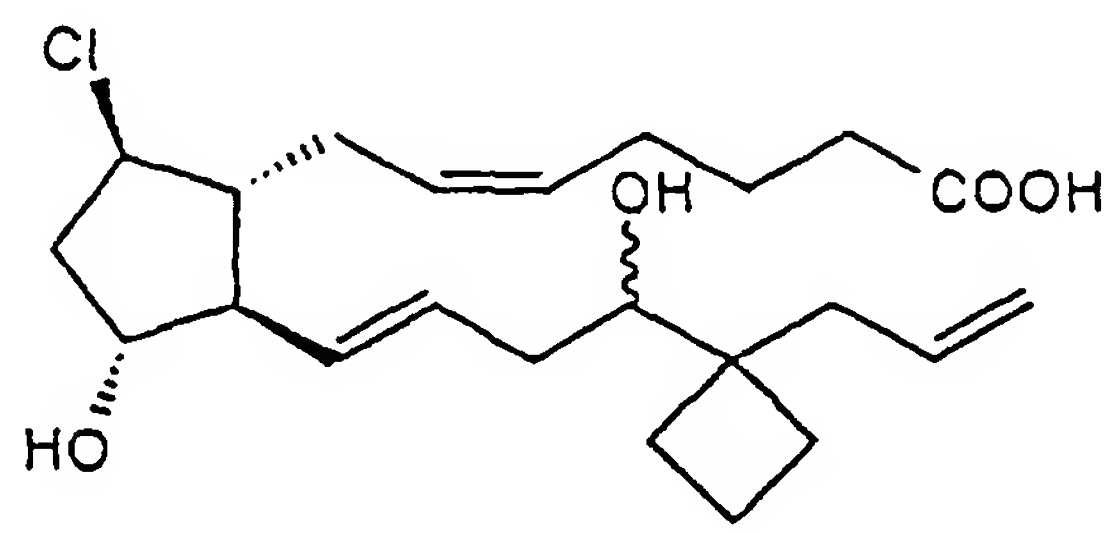
Example 17(1)~17(6)

[0230] By the same procedure as provided in example 17, using the compound prepared in example 16(1)-16(6), compounds of the present invention having the following physical data were obtained.

Example 17(1)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13,19-trienoic acid

[0231]



more polar

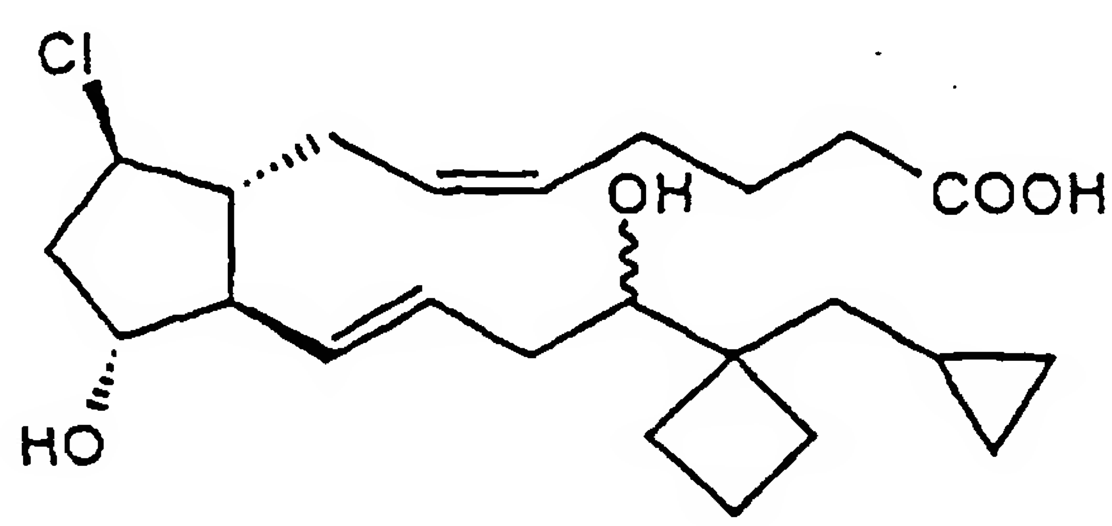
TLC: Rf 0.44 (ethyl acetate : hexane : acetic acid = 6:3:0.1);

NMR ($CDCl_3$): δ 6.95 (1H, ddt, J=17.0, 10.0, 2.0 Hz), 5.70-5.32 (4H, m), 5.20-5.00 (2H, m), 4.20-4.00 (2H, m), 3.59 (1H, dd, J=10.0, 2.0 Hz), 2.36 (2H, t, J=7.0 Hz), 2.40-1.60 (20H, m).

Example 17(2)

(5Z,9β,11α,13E)-17,17-propano-19,20-methano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid

[0232]



more polar

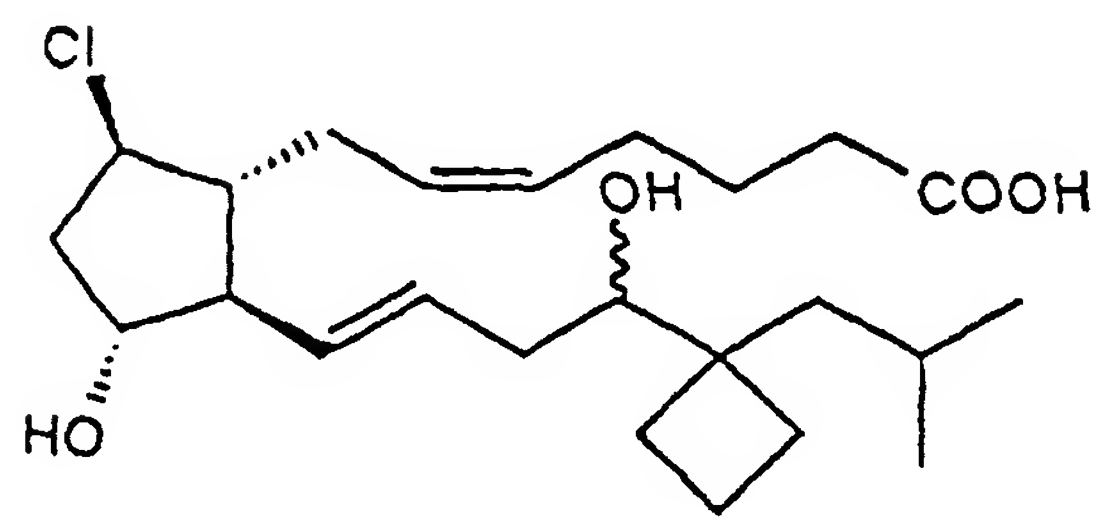
TLC: Rf 0.31 (hexane: ethylacetate: acetic acid = 3.2,0.05);

NMR($CDCl_3$): δ 5.60 (1H, ddd, J=15.4, 7.6, 5.4 Hz), 5.55-5.35 (3H, m), 4.20-3.98 (2H, m), 4.20-3.00 (3H, br), 3.71 (1H, dd, J=10.4, 2.2 Hz), 2.40-1.60 (18H, m), 2.36 (2H, t, J=6.9 Hz), 1.51 (1H, dd, J=14.2, 6.8 Hz), 1.37 (1H, dd, J=14.2, 6.2 Hz), 0.90-0.65 (1H, m), 0.57-0.45 (2H, m), 0.15-0.05 (2H, m).

Example 17(3)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19-methylprosta-5,13-dienoic acid

[0233]



more polar

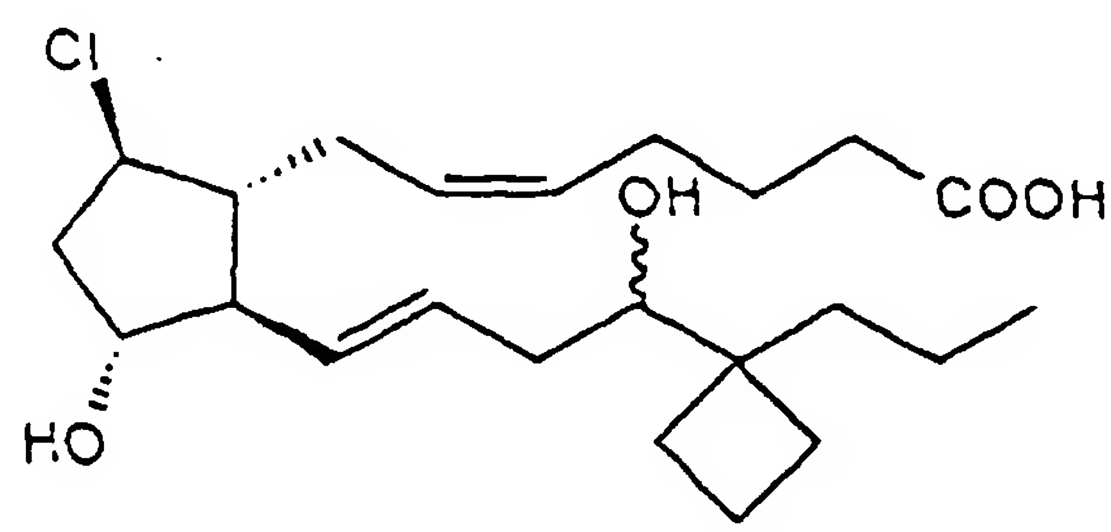
TLC: Rf 0.34 (hexane : ethyl acetate : acetic acid = 3:2:0.05);

NMR ($CDCl_3$): δ 5.60 (1H, ddd, J=15.4, 8.2, 5.6 Hz), 5.55-5.35 (3H, m), 4.20-3.98 (2H, m), 4.20-3.00 (3H, br), 3.65 (1H, dd, J=10.2, 2.2 Hz), 2.40-1.65 (19H, m), 2.36 (2H, t, J=7.1 Hz), 1.55 (1H, dd, J=14.2, 6.6 Hz), 1.33 (1H, dd, J=14.2, 6.2 Hz), 0.92 (3H, d, J=6.6 Hz), 0.91 (3H, d, J=6.6 Hz).

Example 17(4)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid

[0234]



less polar

TLC: Rf 0.33 (hexane : ethyl acetate : acetic acid = 3:2:0.05);

NMR ($CDCl_3$): δ 5.60 (1 H, ddd, J=15.4, 7.8, 5.6 Hz), 5.55-5.37 (3H, m), 4.20-4.00 (2H, m), 4.20-3 00 (3H, br), 3.60 (1H, dd, J=10.0, 2.2 Hz), 2.40-1.20 (22H, m), 2.35 (2H, t, J=6.9 Hz), 0.94 (3H, t, J=6.8 Hz). more polar

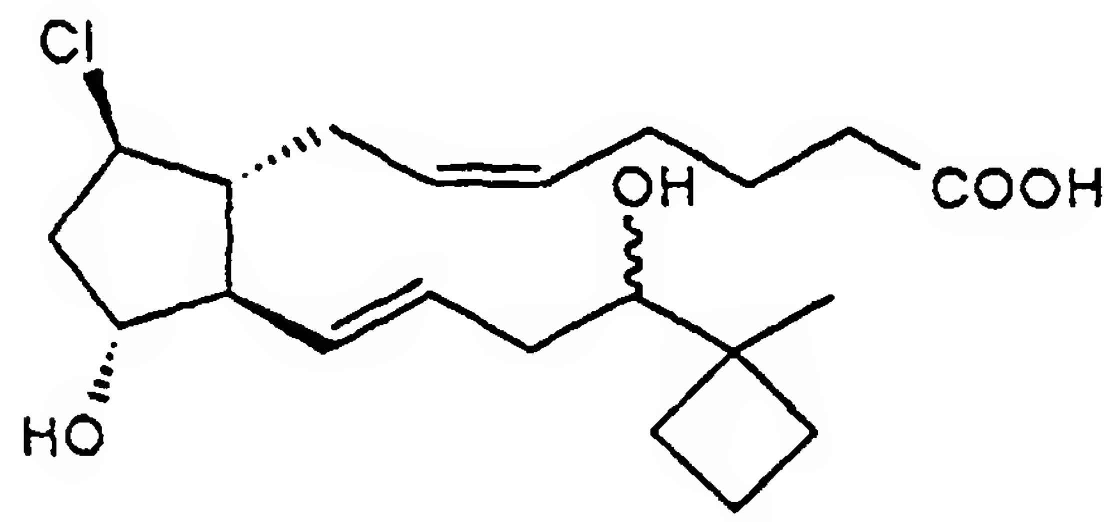
TLC: Rf 0.31 (hexane : ethyl acetate : acetic acid = 3:2:0.05);

NMR($CDCl_3$): δ 5.58 (1H, ddd, J=15.4, 7.6, 5.4 Hz), 5.55-5.35 (3H, m), 4.20-4.00 (2H, m), 4.00-3.00 (3H,br), 3.57 (1H, dd, J=10.2, 2.2 Hz), 2.40-1.20 (22H, m), 2.36 (2H, t, J=6.9 Hz), 0.94 (3H, t, J=6.8 Hz).

Example 17(5)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19,20-dinorprosta-5,13-dienoic acid

[0235]



more polar

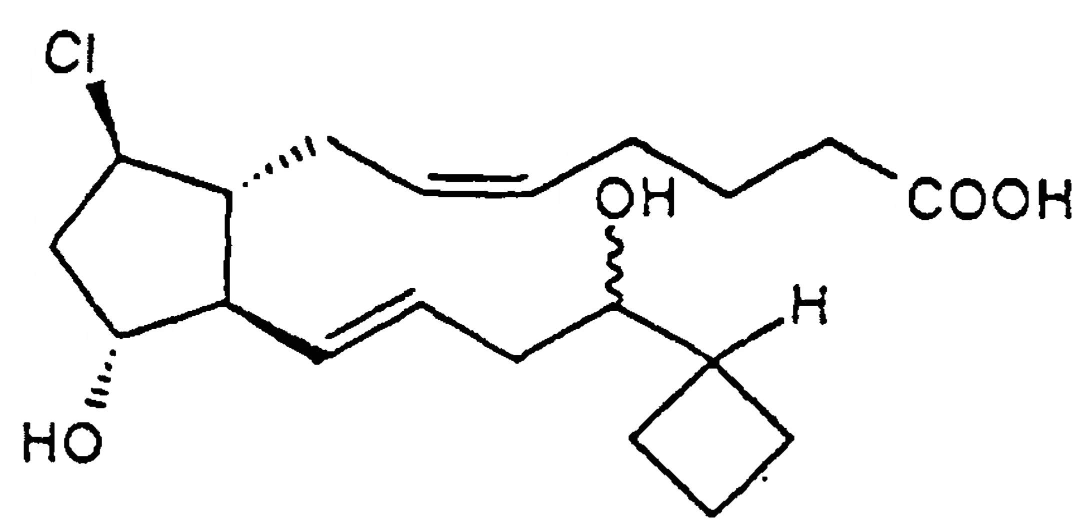
TLC: Rf 0.32 (hexane : ethyl acetate : acetic acid = 2 : 3 : 0.04);

NMR ($CDCl_3$) : δ 5.60 (1H, ddd, J=15, 8, 6Hz), 5.55-5.35 (3H, m), 4.20-4.00 (2H, m), 4.00-3.00 (3H, br), 3.57 (1H, dd, J=10, 2Hz), 2.40-1.50 (20H, m), 1.14 (3H, s)

Example 17(6)

(5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-18,19,20-trinorprosta-5,13-dienoic acid

[0236]



more polar

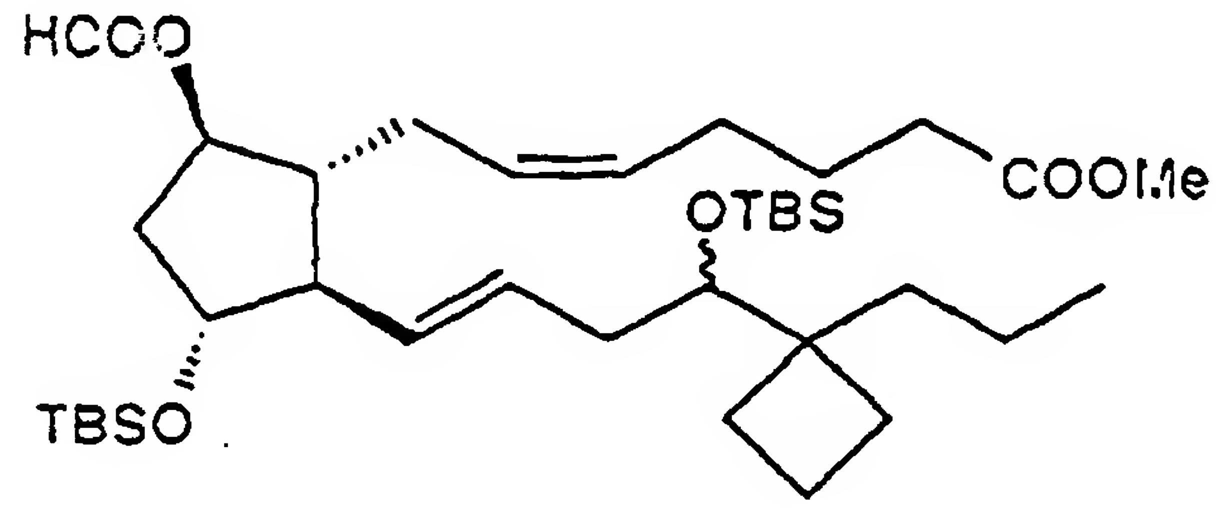
TLC: Rf 0.25 (hexane : ethyl acetate : acetic acid = 2 : 3 : 0.04);

NMR ($CDCl_3$) : δ5.59 (1H, ddd, J=15, 8, 6Hz), 5.54-5.33 (3H, m), 4.20-3.98 (2H, m), 4.00-3.00 (3H, br), 3.62-3.50 (1H, m), 2.60-1.55 (21H, m).

Reference example 26

(5Z,9β,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-formyloxy-prosta-5,13-dienoic acid · methylester

[0237]



[0238] To a stirred solution of the compound prepared in reference example 16 (330 mg) in THF (1.5 ml) was added formic acid (25 ml) and triphenylphosphine (160 mg) under an atmosphere of argon. To the mixture was added dropwise DEAD (0.1 ml, diethylazodicarboxylate) at 0 °C. The reaction mixture was stirred for 33 min. The reaction mixture was quenched by addition of water, extracted with ethyl acetate (x3). The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734, 15 ml. ethyl acetate : hexane = 0 : 1 → 1 : 20) to give the title compound (20 mg) as a yellow oil having the following physical data.

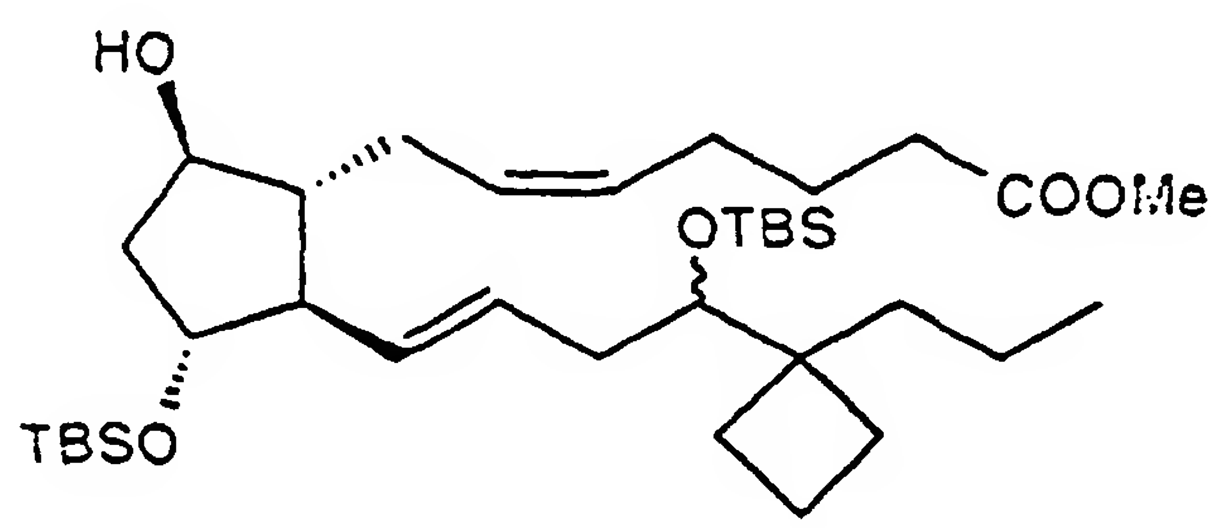
TLC: Rf 0.56 (ethyl acetate : hexane = 1 : 8);

NMR ($CDCl_3$) : δ 7.99 (1H, s), 5.65-5.17 (4H, m), 5.04-4.90 (1H, m), 3.94 (1H, q, J = 7,5 Hz), 3.66 (3H, s), 3.56 (1H, t, J = 5.5 Hz), 2.30 (2H, t, J = 7.5 Hz), 2.40-1.20 (23H, m), 0.91 and 0.90 (9H, each-s), 0.86 (9H, s), 1.00-0.80 (3H, m), 0.06 (3H, s), 0.05 (3H, s), 0.01 (6H, s).

Reference example 27

(5Z,9β,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-hydroxyprosta-5,13-dienoic acid · methylester

[0239]



[0240] To a stirred solution of the compound prepared in reference example 26 (20 mg) in methanol (1 ml) was added ammonia in water solution (0.1 ml) at room temperature under an atmosphere of argon. The reaction mixture was stirred for 30 min, the reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, extracted with ethyl acetate. The extract was washed with water (x2) and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734, 15 ml, ethyl acetate : hexane = 1 : 8 → 1 : 4) to give the title compound (15 mg) as a colorless on having the following physical data

TLC: Rf 0.18 (ethyl acetate hexane = 1.8);

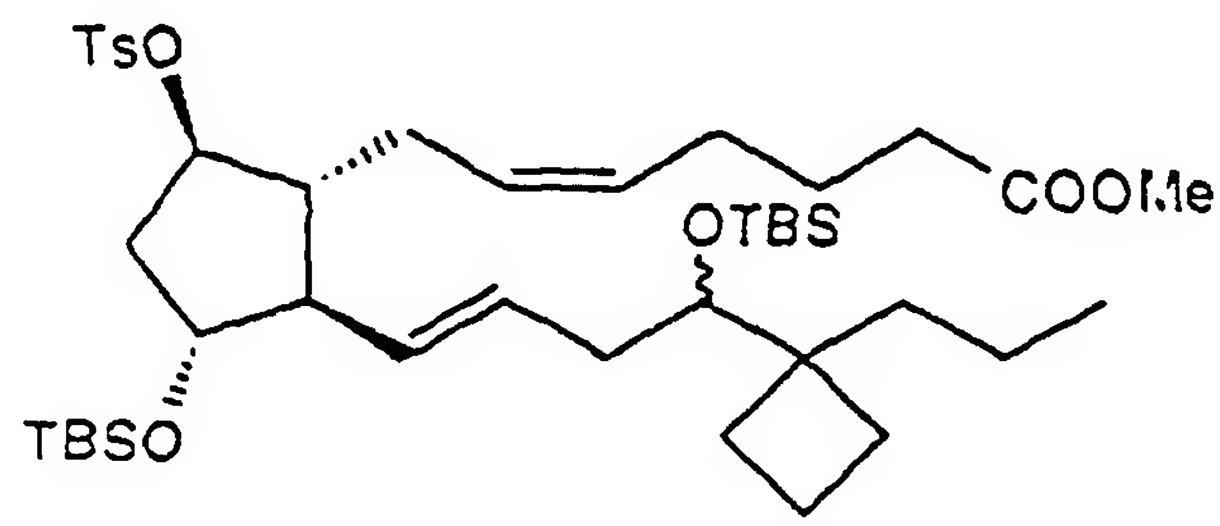
NMR($CDCl_3$) : δ 5.62-5.18 (4H, m), 4.10-3.90 (2H, m), 3.67 (3H, s), 3.55 (1H, t, J = 5.5 Hz), 2.32 (2H, t, J = 8.0

Hz), 2 40-1.20 (23H, m), 1.00-0.80 (3H, m), 0.90 and 0.89 (9H, each-s), 0.86 (9H, s), 0.06 (3H, s), 0.04 (3H, s), 0.01 (6H, s).

Reference example 28

(5Z,9β,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-tosyloxyprosta-5,13-dienoic acid · methylester

[0241]



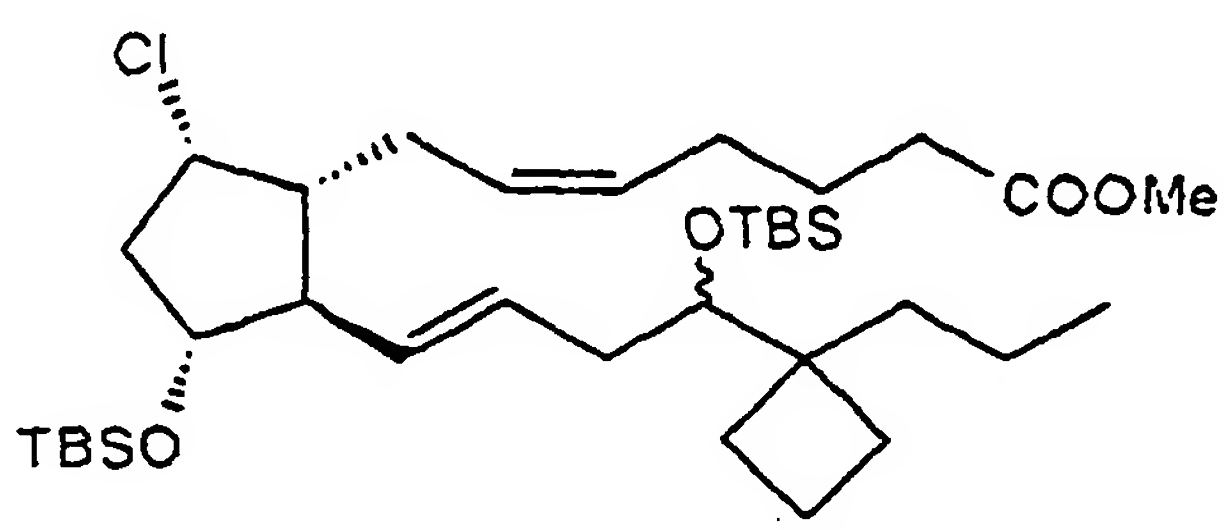
[0242] By the same procedure as provided in reference example 24, using the compound prepared in reference example 27, title compound having the following physical data was obtained.

TLC: Rf 0.47(ethyl acetate : hexane = 6 : 1).

Reference example 29

(5Z,9α,11α,13E)-17,17-propane-11,16-bis(t-butyldimethylsilyloxy)-9-chloroprosta-5,13-dienoic acid · methylester

[0243]



[0244] By the same procedure as provided in reference example 25, using the compound prepared in reference example 28, title compound having the following physical data was obtained

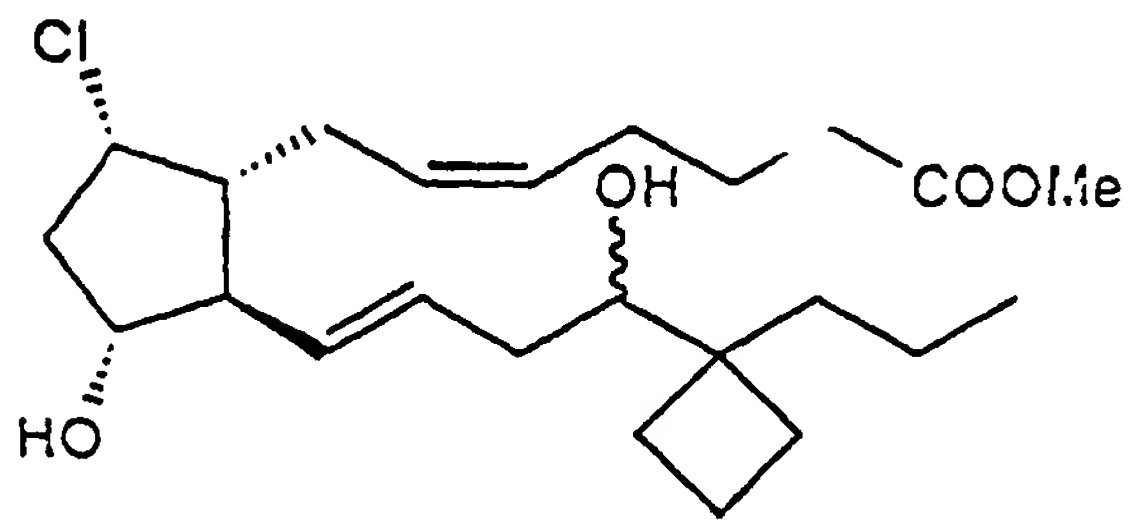
TLC: Rf 0.45(ethyl acetate : hexane = 1 . 20);

NMR ($CDCl_3$) : δ 5.72-5.10 (4H, m), 4.35-4.25 (1H, m), 3.95-3.75 (1H, m), 3.66 (3H, s), 3.57 (1H, t, J=5.5 Hz), 2.54 (2H, ddd, J=15.0, 9.0, 6.0 Hz), 2.50-1.20 (21H, m), 2.31 (2H, t, J=8.0 Hz), 1.00-0.80 (3H, m), 0.91 and 0.90 (9H, each s), 0.86 (9H, s), 0.10-0.00 (6H, m), 0.01 (6H, s).

Example 18

(5Z,9α,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-prosta-5,13-dienoic acid · methylester

[0245]



[0246] By the same procedure as provided in example 1, using the compound prepared in reference example 25, compound of the present invention having the following physical data was obtained. less polar

TLC: Rf 0.56(ethyl acetate : hexane = 1 : 1);

NMR($CDCl_3$) : δ 5.66 (1H, ddd, J=15.5, 8.0, 6.0 Hz), 5.50-5.30 (3H, m), 4.38 (1H, t, J=5.0 Hz), 4.10-3.90(1H, m), 3.67 (3H, s), 3.56 (1H, dd, J=10.0, 2.0 Hz), 2.70-1.20 (22H, m), 2.33 (2H, t, J=8.0 Hz), 0.94 (3H, t, J=7.0 Hz).

more polar

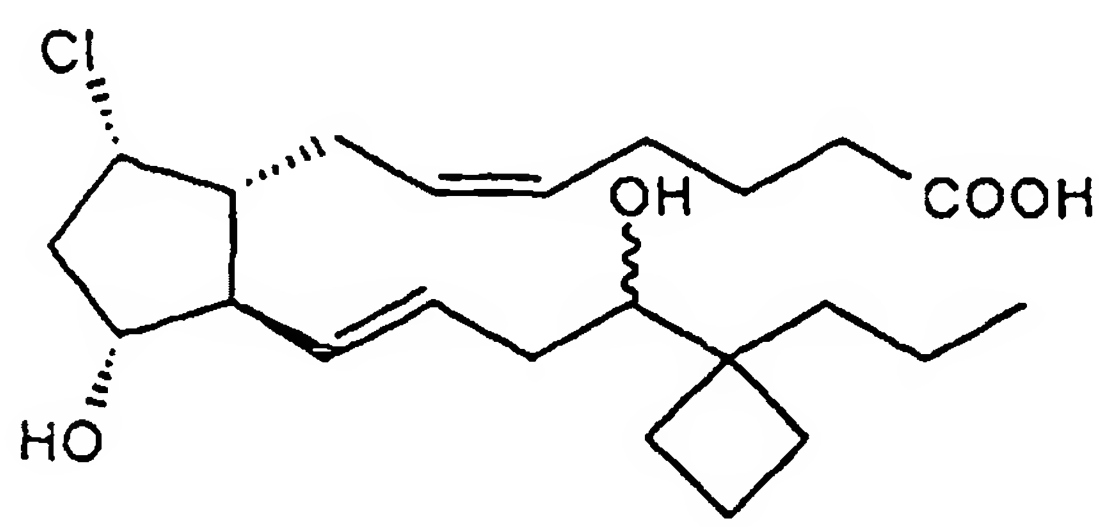
TLC: Rf 0.47(ethyl acetate : hexane = 1 : 1);

NMR($CDCl_3$) : δ 5.66 (1H, ddd, J = 15.5, 8.0, 5.5 Hz), 5.50-5.30 (3H, m), 4.38 (1H, t, J=5.0 Hz), 3.98 (1H, ddd, J=9.0, 6.0, 2.5 Hz), 3.67 (3H, s), 3.56 (1H, dd, J=10.0, 2.0 Hz), 2.70-1.20 (22H, m), 2.32 (2H, t, J-7.5 Hz), 0.94 (3H, t, J=7.0 Hz).

Example 19

(5Z,9α,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-prosta-5,13-dienoic acid

[0247]



[0248] By the same procedure as provided in example 15, using the compound prepared in example 18, compound of the present invention having the following physical data was obtained.

less polar

TLC: Rf 0.47 (ethyl acetate : hexane = 2:1);

NMR ($CDCl_3$): δ 5.75-5.30 (4H, m), 4.44 (1H, t, J=4.5 Hz), 3.97 (1H, ddd, J=9.0, 6.0, 3.5 Hz), 3.58 (1H, dd, J=10.0, 2.0 Hz), 2.70-1.20 (22H, m), 2.34 (2H, t, J=6.5 Hz), 0.94 (3H, t, J=6.5 Hz),

more polar

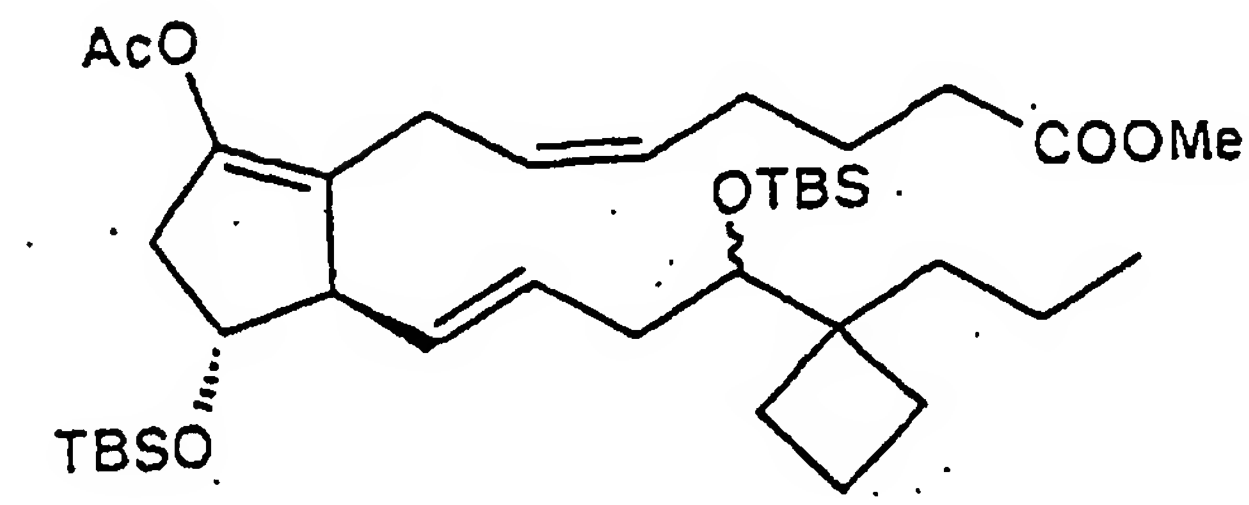
TLC: Rf 0.47 (ethyl acetate : hexane = 2:1);

NMR ($CDCl_3$): δ 5.67 (1H, dt, J=15.5, 6.5 Hz), 5.60-5.30 (3H, m), 4.42 (1H, t, J=5,0 Hz), 4.03 (1H, ddd, J=9.0, 6.0, 3.0 Hz), 3.66 (1H, dd, J=9.5, 2.5 Hz), 2.70-1.20 (22H, m), 2.34 (2H, t, J=7.0 Hz), 0.94 (3H, t, J=6.5 Hz).

Reference example 30

(5Z,8Z,11α,13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-9-acetyloxy-prosta-5,8,13-trienoic acid · methylester

[0249]



[0250] To a solution of (1E, 4RS)-1-iodo-4-t-butyldimethylsilyloxy-5,5-propanoocta-1-ene (407 mg) in anhydrous ether (3 ml) was added dropwise t-butyllithium (1.21 ml; 1.7 M pentane solution) at -78 °C. After the mixture was stirred for 60 min, to the mixture was added dropwise lithium 2-thienylcyanocuprate (4.8 ml; 0.25 M tetrahydrofuran solution) at same temperature. After the mixture was stirred for 20 min, to the mixture was added dropwise a solution of (5Z)-7-((3R)-3-t-butyldimethylsilyloxy-5-oxocyclopenta-1-ene (234 mg) in ether (4 ml). After the mixture was warmed up to -20 °C for 45 min, to the mixture was added acetic anhydride (1.88 ml). The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, extracted with hexane. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Wako gel C-200, 40 ml, hexane:ethyl acetate = 1:0 →50:1→20:1) to give the title compound (324 mg) having the following physical data.

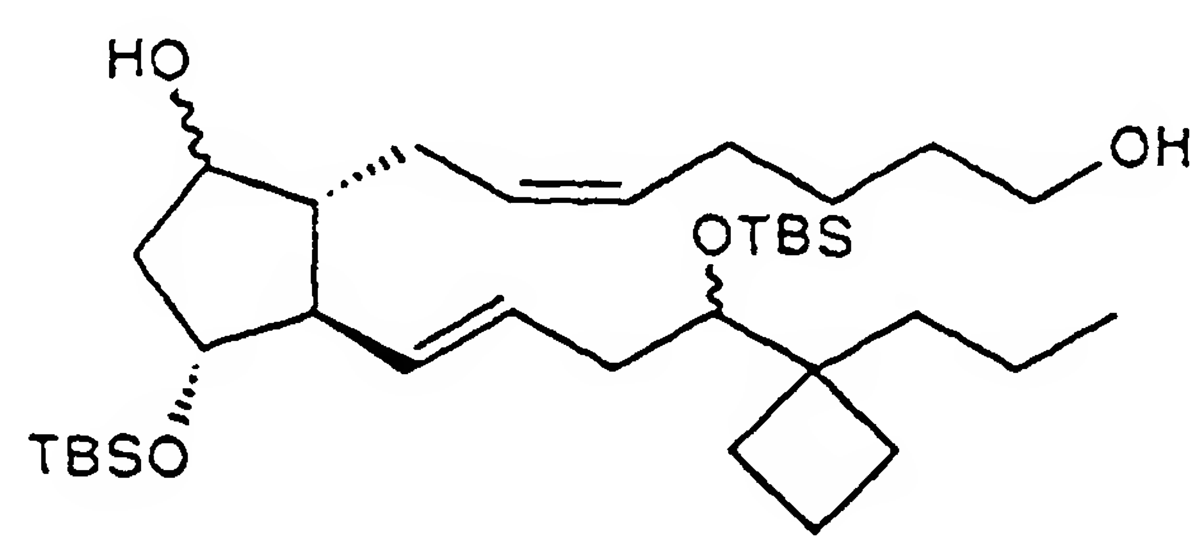
TLC: Rf 0.50 (hexane:ethyl acetate = 9:1);

NMR ($CDCl_3$) : δ 5.70-5.45 (1H,m), 5.45-5.15 (3H, m), 4.14-4.02 (1H,m), 3.66 (3H,s), 3.55 (1H, t, J=5.1 Hz), 3.05-2.92 (1H,m), 2.99-2.68 (2H, m), 2.60-2.30 (2H,m), 2.30 (2H,t,J=7.6 Hz), 2.20-1.20 (16H,m), 2.13 (3H,s), 1.00-0.90 (21H,m), 0.10-0.00 (12H,m).

Reference example 31

(5Z, 11α, 13E)-17,17-propano-11,16-bis(t-butyldimethylsilyloxy)-1, 9-dihydroxy-prosta-5,13-diene

[0251]



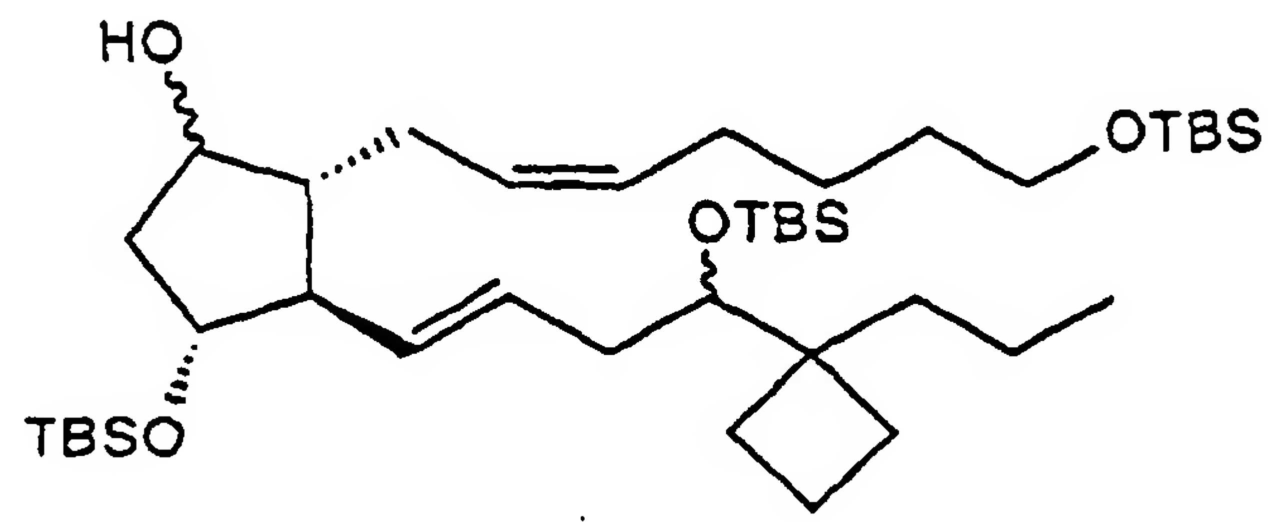
[0252] To a solution of the compound prepared in reference example 3 (174 mg) in THF (3 ml) was added dropwise DIBAL (1.16 ml; 0.95 M hexane solution) at -78 °C. The reaction mixture was stirred at 0 °C for 30 min, and stirred at room temperature for 30 min. To the reaction mixture was added dropwise a saturated aqueous solution of sodium sulfate (0.3 ml), diluted with ether. The mixture was stirred at room temperature for 30 min, the reaction mixture was dried over anhydrous magnesium sulfate and concentrated to give the title compound (160 mg) having the following physical data.

TLC: Rf 0.40 (9α-OH form) and 0.24 (9β-OH form) (hexane : ethyl acetate = 3 : 1).

Reference example 32

(5Z,11α,13E)-17,17-propano-1,11,16-tris(t-butyldimethylsilyloxy)-9-hydroxyprosta-5,13-diene

[0253]



[0254] To a solution of the compound prepared in reference example 31 (160 mg) and pyridine (44 ml) in dichloromethane (3 ml) was added TBSCl (45 mg; t-butyldimethylsilyl chloride) under cooling with ice. The reaction mixture was stirred at room temperature for overnight. To the reaction mixture was added pyridine (50 ml) and TBSCl (50 mg). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium hydrogencarbonate, extracted with hexane. The extract was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Merck 7734, 20 g, hexane : ethyl acetate = 1 : 0 → 20:1 → 10 : 1) to give the title compound (total 142 mg) having the following physical data.

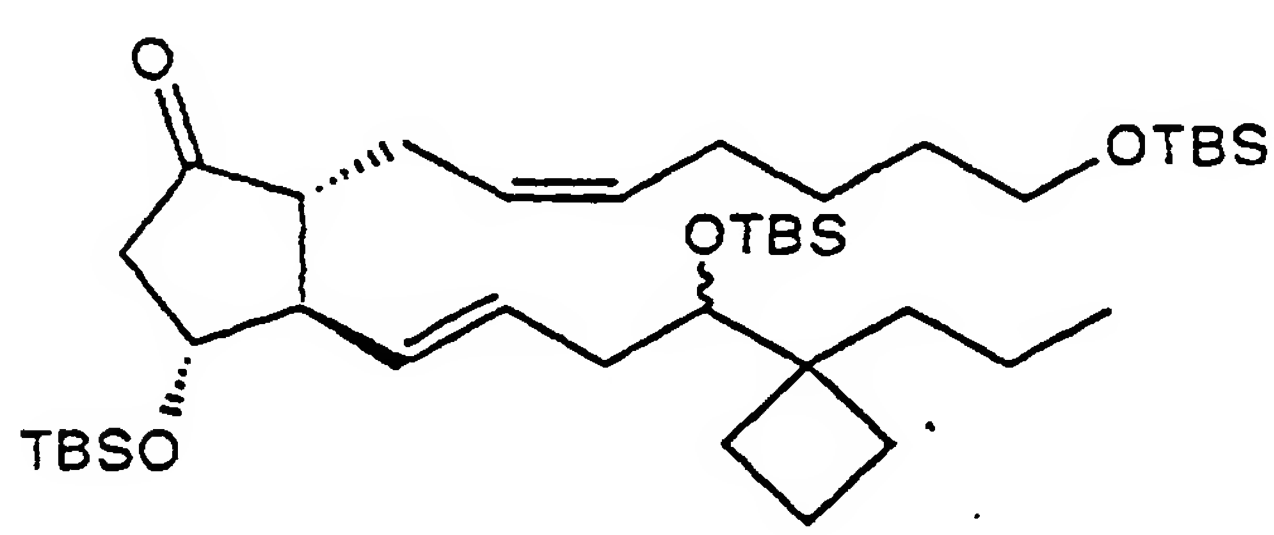
TLC: Rf 0.62 (9α-OH form) and 0.46 (9β-OH form) (hexane : ethyl acetate = 9 : 1);

NMR ($CDCl_3$) : δ 5.60-5.15 (4H, m), 4.10-3.90 (2H, m), 3.65-3.45 (3H, m), 2.40-1.20 (24H, m), 1.00-0.90 (30H, m), 0.10-0.00 (18H, m).

Reference example 33

(5Z,11α,13E)-17,17-propano-1,11,16-tris(t-butyldimethylsilyloxy)-9-oxoprosta-5,13-diene

[0255]



[0256] To a solution of oxalyl chloride (33 ml) in dichloromethane (0.5 ml) was added dropwise dimethylsulfoxide (55 ml) at -78 °C. After the mixture was stirred for 10 min, to the mixture was added dropwise a solution of the compound prepared in reference example 32 (140 mg) in dichloromethane (3 ml). After the mixture was warmed up to -40 °C for 1 hour, to the mixture added dropwise triethylamine (0.22 ml). The reaction mixture was warmed up to -10 °C for 1 hour. The reaction mixture was quenched by addition of water and 2N aqueous solution of hydrochloric acid (0.7 ml), extracted with hexane. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Wako gel C-200, 15 g, hexane:ethyl acetate = 1:0 → 30:1) to give the title compound (112 mg) having the following

physical data.

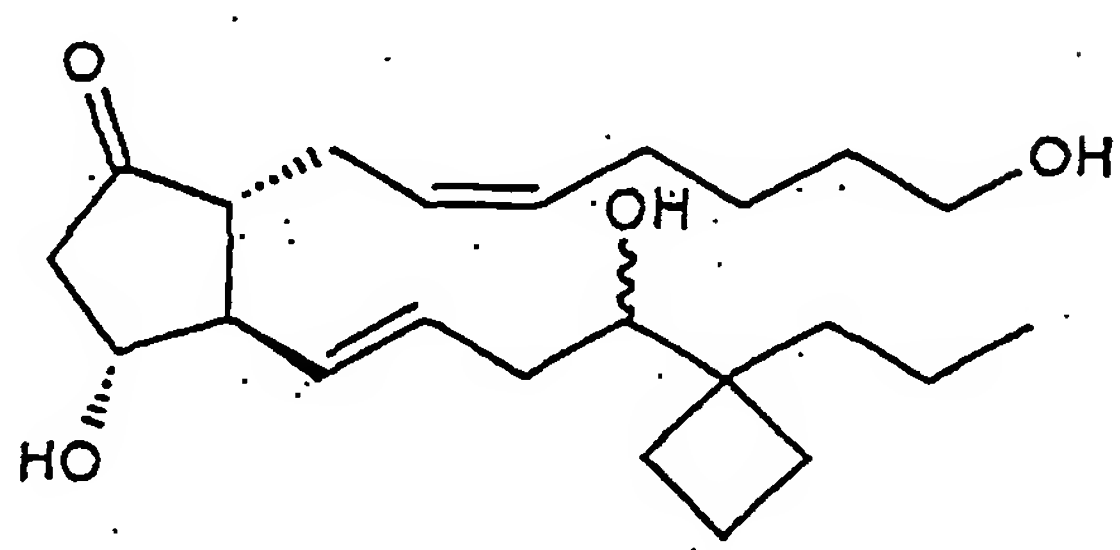
TLC: Rf 0.80 (hexane:ethyl acetate = 9:1);

NMR ($CDCl_3$) : δ 5.70-5.20 (4H,m), 4.05-3.90 (1H,m), 3.59 (2H,t,J=6.3 Hz), 3.58-3.50 (1H,m), 2.65-1.20 (24H, m), 1.00-0.90 (30H,m) 0.10-0.00 (18H,m).

Example 20

(5Z,11α,13E)-17,17-propane-11,16-dihydroxy-9-oxoprosta-5, 13-diene-1-ol

[0257]



[0258] By the same procedure as provided in example 1, using the compound prepared in reference example 33, compounds of the present invention having the following physical data were obtained.

less polar

TLC: Rf 0.40 (hexane:ethyl acetate:methanol = 1:3 : 0.04) ;

NMR ($CDCl_3$) : δ 5.76 (1H, dt, J=15.2, 7.0 Hz), 5.45 (1H,dd, J=15.2, 7.8 Hz), 5.50-5.20 (2H,m), 4.12-3.98 (1H, m), 3.70-3.59 (2H,m), 3.50 (1H,dd, J=10.4, 2.6 Hz), 2.74 (1H,ddd, J=18.2, 7.2, 1.0 Hz), 2.55-1.20 (26H,m), 0.94 (3H, t J=7.4 Hz).

more polar

TLC: Rf 0.37 (hexane:ethyl acetate:methanol = 1:3: 0.04) ;

NMR ($CDCl_3$) : δ 5.71 (1H,ddd, J=15.4, 8.2, 5.8 Hz), 5.50-5.20 (3H,m), 4.10-3.95 (1H,m), 3.64 (2H,t J=6.4 Hz), 3.56 (1H,dd, J=10.2, 2.4 Hz), 2.73 (1H,ddd, J=18.0, 7.6, 1.0 Hz), 2.50-1.20 (26H, m), 0.94(3H,t, J=6.8 Hz).

Formulation example

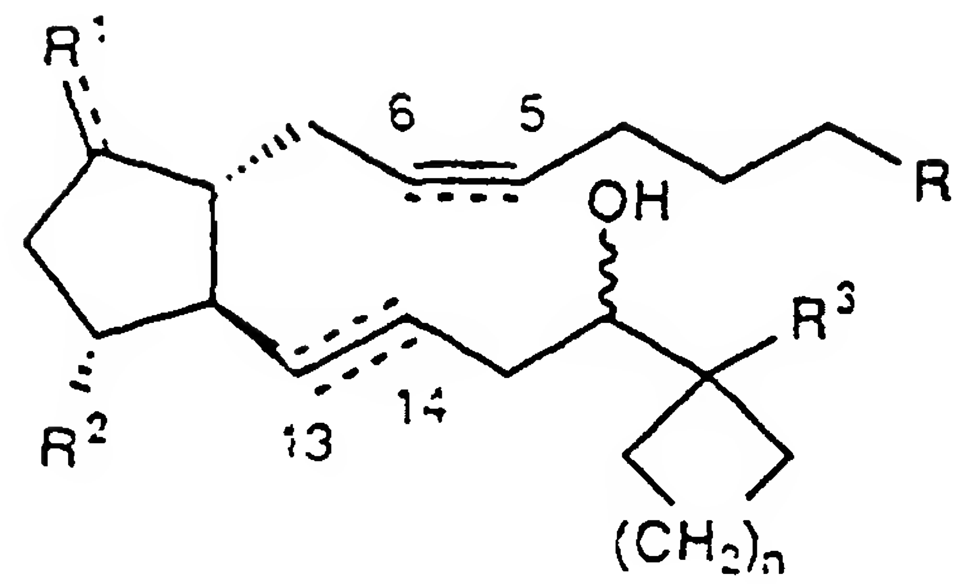
Formulation example 1

[0259] The following compounds were admixed in conventional method, dried, added microcrystalline cellulose, mixed until homogeneous and punched out to obtain 100 tablets each containing 30 μg of active ingredient.

- The solution of (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-denoic acid (3 mg) in ethanol 10 mL
- Magnesium stearate 100 mg
- silicon dioxide 20 mg
- talc 10 mg
- Carboxymethylcellulose calcium 200 mg
- Microscrystalline cellulose 5.0 g

Claims

1. An ω-cycloalkyl-prostaglandin E_2 derivative of formula (I)



(I)

wherein R is carboxy or hydroxymethyl;

R^1 is oxo, methylene or halogen atom;
R^2 is hydrogen atom, hydroxy or C1-4 alkoxy;
R^3 is hydrogen atom, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from (1)-(5):

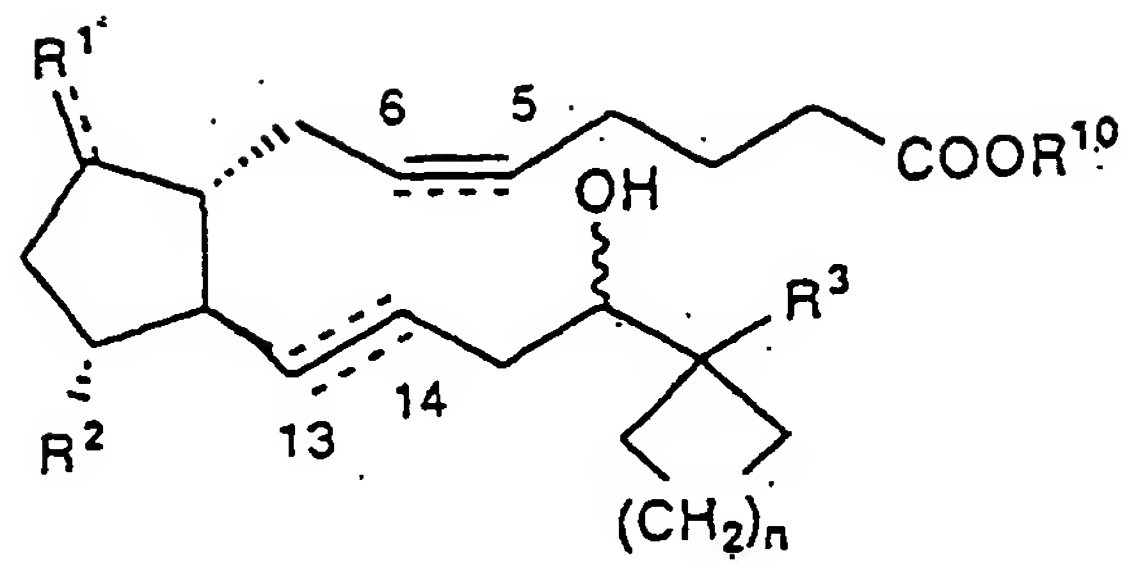
(1) halogen atom,
(2) C1-4 alkoxy,
(3) C3-7 cycloalkyl,
(4) phenyl, and
(5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro and trifluoromethyl;

n is 0-4;

is single bond or double bond;

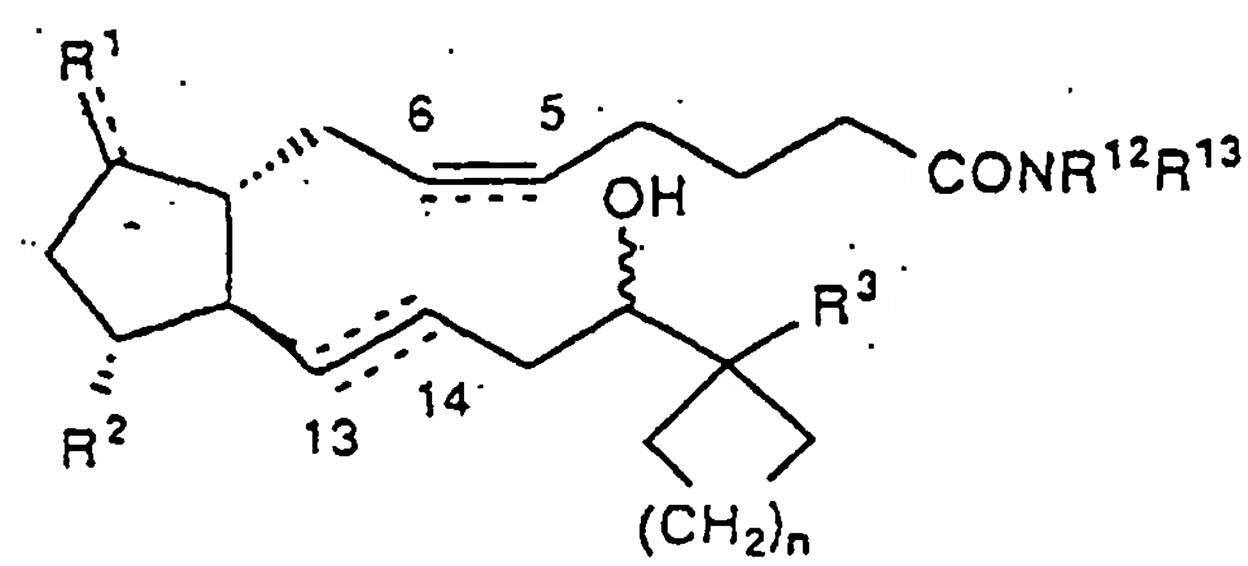
is double bond or triple bond; and

is a single bond, double bond or triple bond;
and wherein the double bond at the 13-14 position, when present, is in the E, Z or EZ mixture form;
with the proviso that when the 5-6 position is a triple bond, the 13-14 position is not a triple bond;
or a non-toxic salt thereof, cyclodextrin clathrate thereof, or prodrug thereof of formula (IA)



(IA)

wherein R^{10} is C1-6 alkyl and the other symbols are as defined above, or of formula (IB)



(IB)

wherein R^{12} and R^{13} each, independently, is hydrogen atom or C1-6 alkyl and the other symbols are as defined above.

2. A compound according to claim 1, wherein R is carboxy.

3. A compound according to claim 1, wherein R is hydroxymethyl.

4. A compound according to claim 1 which is

(1) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-dienoic acid . methylester,
(2) (5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-ene-13-ynoic acid · methylester,
(3) (11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-13-ene-5-ynoic acid · methylester,
(4) (5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-enoic acid · methylester,
(5) (5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester,
(6) (5Z,11α,13E)-11,16-dihydroxy-20-ethyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester,
(7) (5Z,11α,13E)-20-chloro-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-dienoic acid · methylester,
(8) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-18-phenyl-17,17-propano-19,20-dinorprosta-5,13-dienoic acid · methylester,
(9) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13,19-trienoic acid · methylester,
(10) (5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-diene-19-ynoic acid · methylester,
(11) (5Z,11α,13E)-17,17-butano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester,
(12) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-pentanoprosta-5,13-dienoic acid · methylester,
(13) (5Z,11α,13E)-18-cyclohexyl-11,16-dihydroxy-9-oxo-17,17-propano-19,20-dinorprosta-5,13-dienoic acid · methylester,
(14) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-dienoic acid · methylester,
(15) (5Z,11α,13E)-17,17-propano-19,20-methano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester,
(16) (5Z,11α,13E)-17,17-propano-20,20-methylene-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methyl-

ester,
(17) (5Z,11α,13E)-17,17-propano-20-methoxy-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester,
(18) (5Z,11α,13E)-17,17-propano-20-fluoro-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester,
(19) (5Z,11α,13E)-17,17-propano-19-methyl-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid · methylester,
(20) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-20-norprosta-5,13,18-trienoid acid · methylester.
(21) (5Z,13E)-17,17-propano-16-hydroxy-9-oxoprosta-5,13-dienoic acid · methylester.
(22) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13-dienoid acid · methylester,
(23) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-19-methylprosta-5,13-dienoic acid · methylester,
(24) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-19,20-methanoprosta-5,13-dienoic acid · methylester,
(25) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-20-norprosta-5,13-dienoic acid · methylester,
(26) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13,19-trienoic acid · methylester,
(27) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9,9-methyleneprosta-5,13-dienoic acid · methylester.
(28) (5Z,9β,11α,13E)-17,17-propano-1,16-dihydroxy-9-fluoro-prosta-5,13-dienoic acid ·methylester,
(29) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-20-norprosta-5,13-dienoic acid · methylester,
(30) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13,19-trienoic acid · methylester.
(31) (5Z,9β,11α,13E)-17,17-propano-19,20-methano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid · methylester,
(32) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19-methylprosta-5,13-dienoic acid · methylester,
(33) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid · methylester,
(34) (5Z,9α,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-prosta-5,13-dienoic acid · methylester,
(35) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-19,20-dinorprosta-5,13-dienoic acid · methylester,
(36) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-18,19,20-trinorprosta-5,13-dienoic acid · methylester,
(37) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19,20-dinorprosta-5,13-dienoic acid · methylester, or
(38) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-18,19,20-trinorprosta-5,13-dienoic acid · methylester,

in the form of the more or less polar stereoisomer on the 16-position or a mixture thereof.

5. A compound according to claim 1, which is

(1) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid amide,

in the form of the more or less polar stereoisomer on the 16-position or a mixture thereof.

6. A compound according to claim 2, which is

(1) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-dienoic acid,
(2) (5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid,
(3) (5Z,11α,13E)-11,16-dihydroxy-20-ethyl-9-oxo-17,17-propanoprosta-5,13-dienoic acid,
(4) (5Z,11α,13E)-20-chloro-11,16-dihydroxy-9-oxo-17, 17-propanoprosta-5,13-dienoic acid,
(5) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-18-phenyl-17,17-propano-19,20-dinorprosta-5,13-dienoic acid,
(6) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-19-trienoic acid
(7) (5Z,11α,13E)-11,16-dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-diene-19-ynoic acid,
(8) (5Z,11α,13E)-17,17-butano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid,
(9) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-pentanoprosta-5,13-dienoic acid,
(10) (5Z,11α,13E)-18-cyclohexyl-11,16-dihydroxy-9-oxo-17,17-propano-19,20-dinorprosta-5,13-dienoic acid,
(11) (5Z,11α,13E)-11,16-dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-dienoic acid,
(12) (5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-enoic acid,
(13) (5Z,11α,16RS)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5-ene-13-ynoic acid,
(14) (11α,13E)-11,16-dihydroxy-9-oxo-17,17-propanoprosta-13-ene-5-ynoic acid,
(15) (5Z,11α,13E)-17,17-propano-19,20-methano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid,
(16) (5Z,11α,13E)-17,17-propano-20,20-methylene-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid,

(17) (5Z,11α,13E)-17,17-propano-20-methoxy-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid,
(18) (5Z,11α,13E)-17,17-propano-20-fluoro-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid,
(19) (5Z,11α,13E)-17,17-propano-19-methyl-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid,
(20) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-20-norprosta-5,13,18-trienoic acid,
(21) (5Z,11α,13Z)-17,17-propano-11,16-dihydroxy-9-oxoprosta-5,13-dienoic acid
(22) (5Z,13E)-17,17-propano-16-hydroxy-9-exoprosta-5,13-dienoic acid,
(23) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13-dienoic acid,
(24) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-19-methyl-9-oxoprosta-5,13-dienoic acid,
(25) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-19,20-methanoprosta-5,13-dienoic acid,
(26) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxo-20-norprosta-5,13-dienoic acid,
(27) (5Z,11α,13E)-17,17-propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13,19-trienoic acid,
(28) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9,9-methyleneprosta-5,13-dienoic acid,
(29) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-fluoro-prosta-5,13-dienoic acid,
(30) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-20-norprosta-5,13-dienoic acid,
(31) (5Z,9β,11α,3E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13,19-trienoic acid,
(32) (5Z,9b,11α,13E)-17,17-propano-19,20-methano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid,
(33) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19-methylprosta-5,13-dienoic acid,
(34) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13-dienoic acid,
(35) (5Z,9α,11V,13E)-17,17-propane-11,16-dihydroxy-9-chloro-prosta-5,13-dienoic acid,
(36) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-19,20-dinorprosta-5,13-dienoic acid,
(37) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxo-18,19,20-trinorprosta-5,13-dienoic acid,
(38) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-19,20-dinorprosta-5,13-dienoic acid, or
(39) (5Z,9β,11α,13E)-17,17-propano-11,16-dihydroxy-9-chloro-18,19,20-trinorprosta-5,13-dienoic acid,

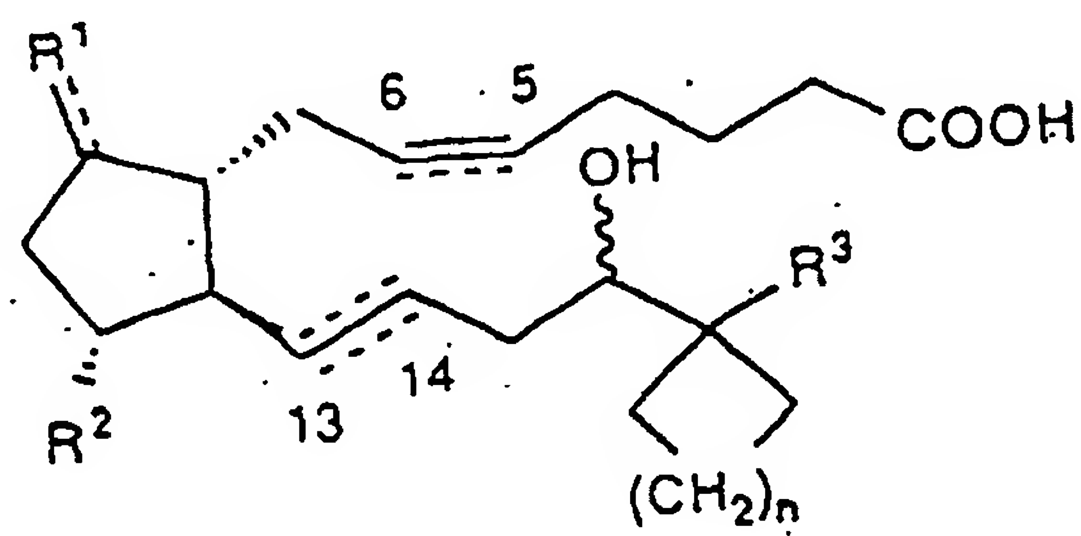
in the form of the more or less polar stereoisomer on the 16-position or a mixture thereof.

7. A compound according to claim 3, which is

(1) (5Z,11α,13E)-17,17-propano-11,16-dihydroxy-9-oxoprosta-5,13-diene-1-ol,

in the form of the more or less polar stereoisomer on the 16-position or a mixture thereof.

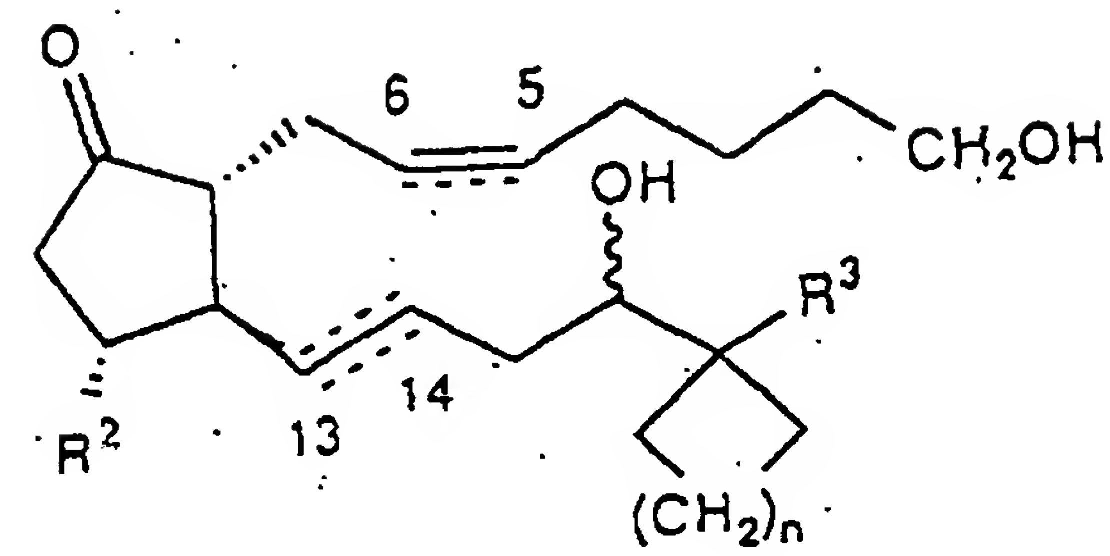
8. A process for the preparation of a compound of formula (I) as defined in claim 1, which is of formula (I-1)



(I-1)

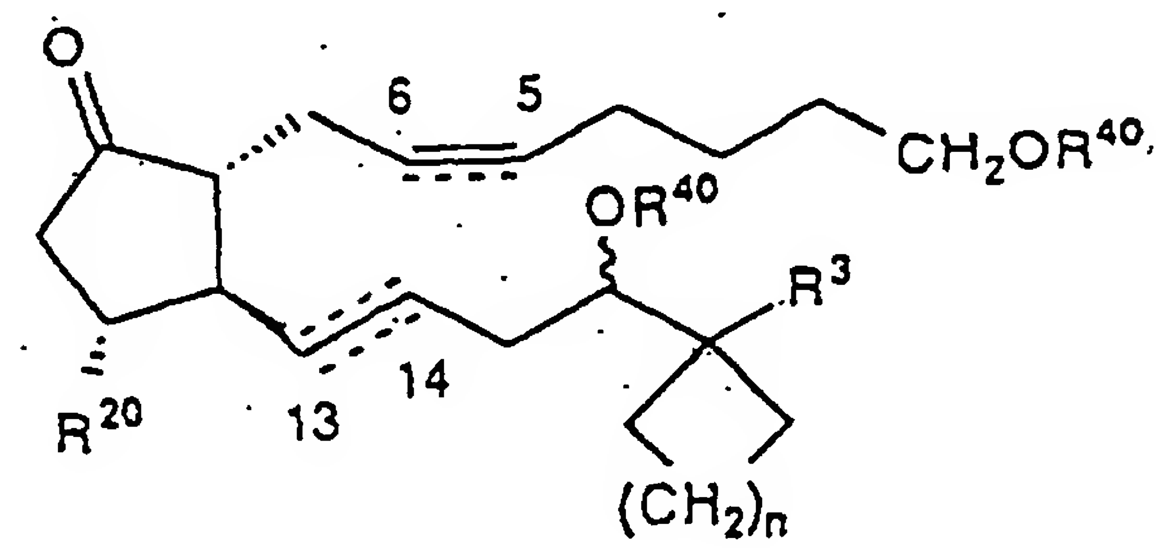
wherein all the symbols are as defined in claim 1, which process comprises hydrolysis using an enzyme or hydrolysis under alkaline conditions of a compound of formula (IA) as defined in claim 1.

9. A process for the preparation of a compound of formula (I) as defined in claim 1, which is of formula (I-2A)



(I-2A)

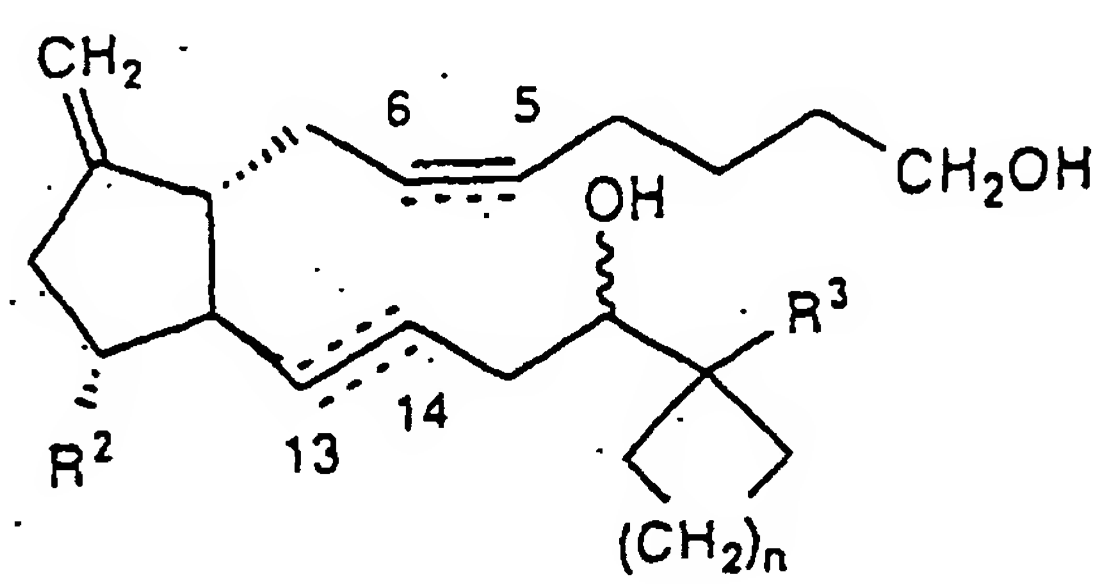
wherein all the symbols are as defined in claim 1, which process comprises elimination under acidic conditions of the protecting group(s) of a compound of formula (IIA)



(IIA)

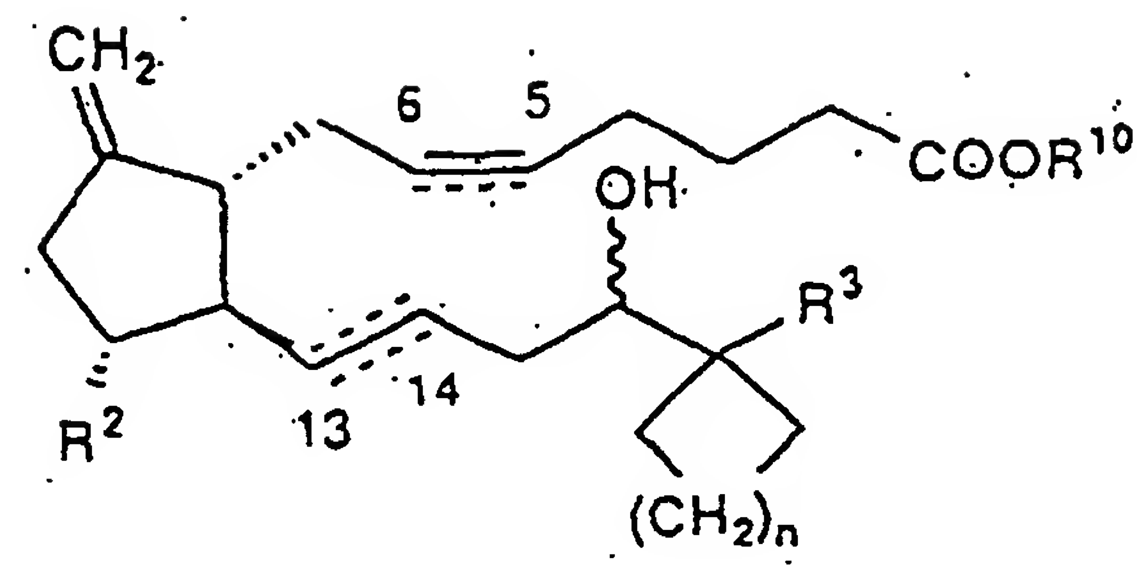
wherein R^{20} is hydrogen atom, hydroxy protecting group which may be eliminated under acidic conditions or C1-4 alkoxy, R^{40} is hydroxy protecting group which may be eliminated under acidic conditions, and the other symbols are as defined in claim 1.

10. A process for the preparation of a compound of formula (I) as defined in claim 1, which is of formula (I-2B)



(I-2B)

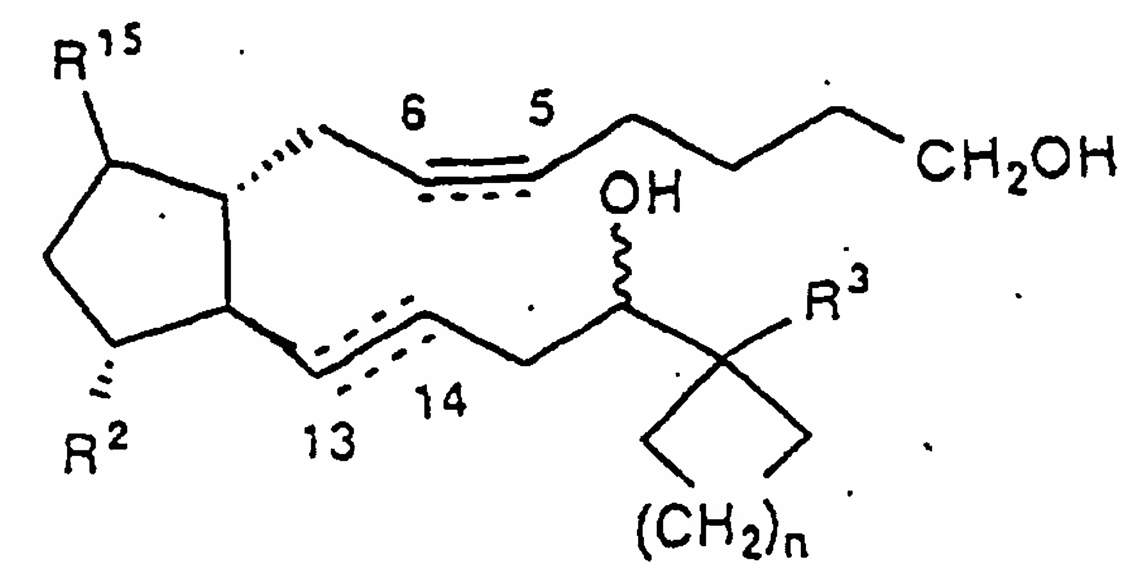
wherein all the symbols are as defined in claim 1, which process comprises reduction of a compound of' formula (IA-4),



(IA-4)

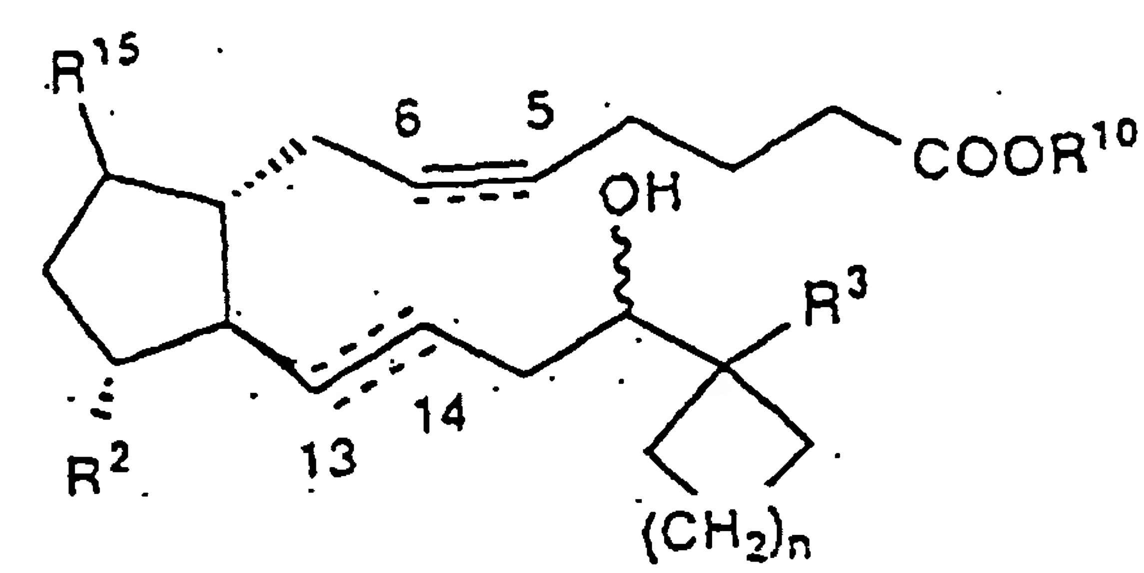
wherein all the symbols are as defined in claim 1.

11. A process for the preparation of a compound of formula (I) as defined in claim 1, which is of formula (I-2C)



(I-2C)

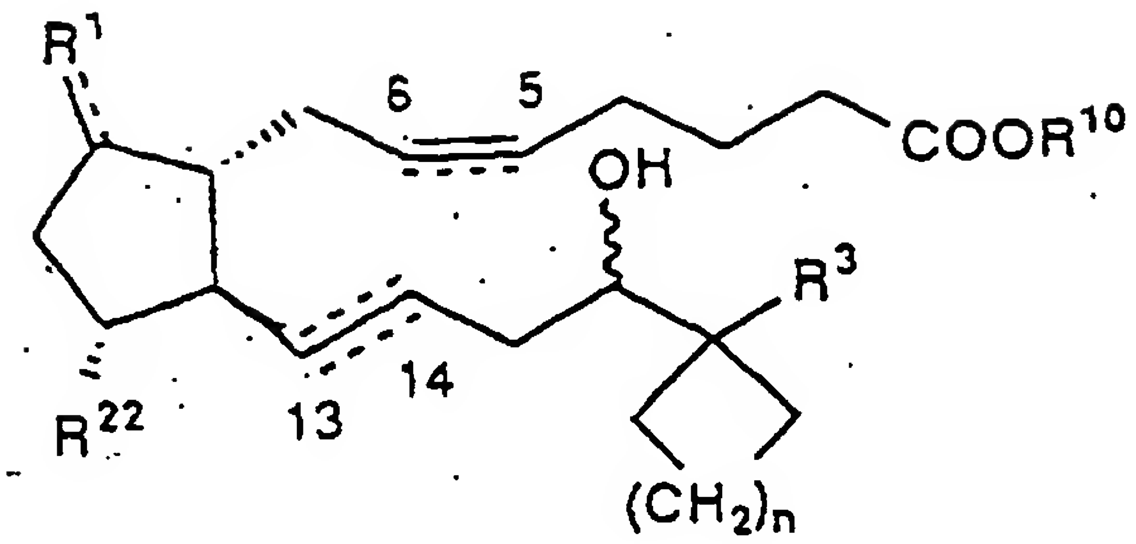
wherein R^{15} is halogen atom and the other symbols are as defined in claim 1, which process comprises reduction of a compound of formula (IA-5)



(IA-5)

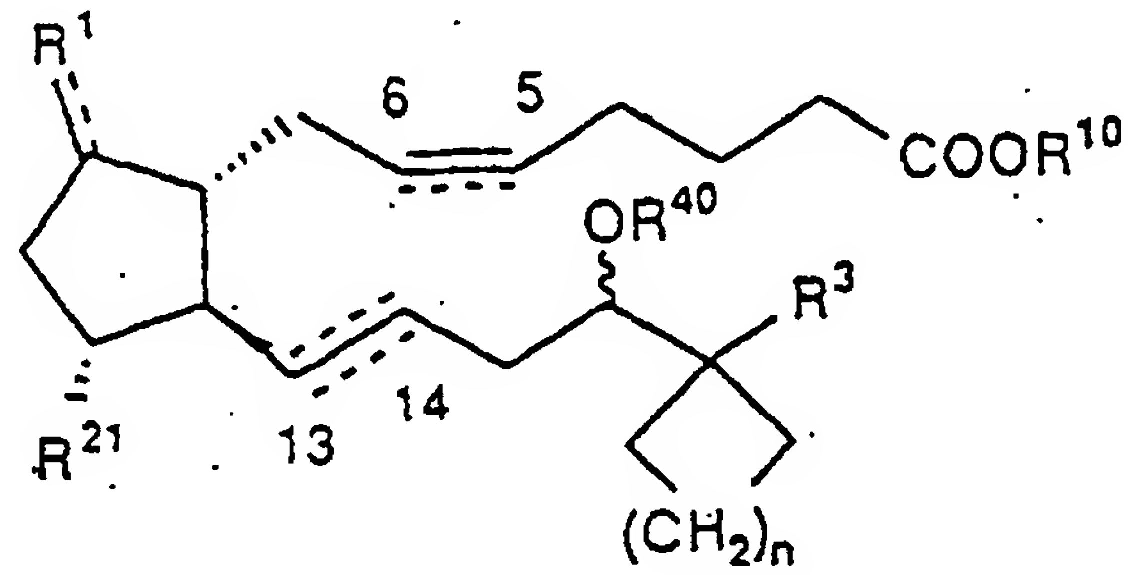
wherein R^{15} is halogen atom, and the other symbols are as defined in claim 1.

12. A process for the preparation of a prodrug compound of formula (IA) as defined in claim 1, which is of formula (IA-1)



(IA-1)

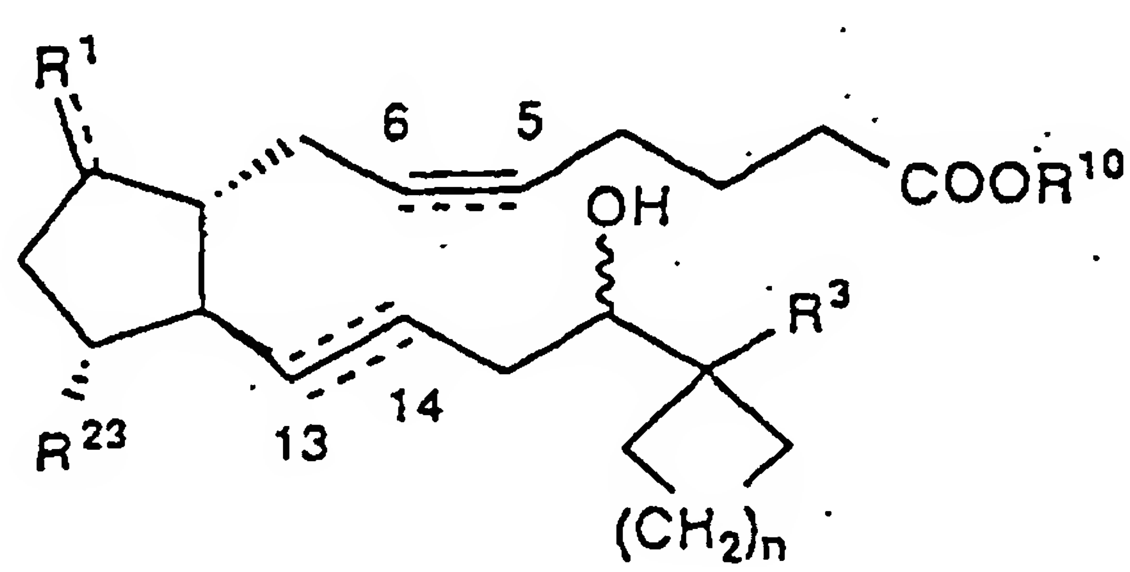
wherein R^{22} is hydrogen atom or hydroxy, and the other symbols are as defined in claim 1, which process comprises hydrolysis under acidic conditions of a compound of formula (III)



(III)

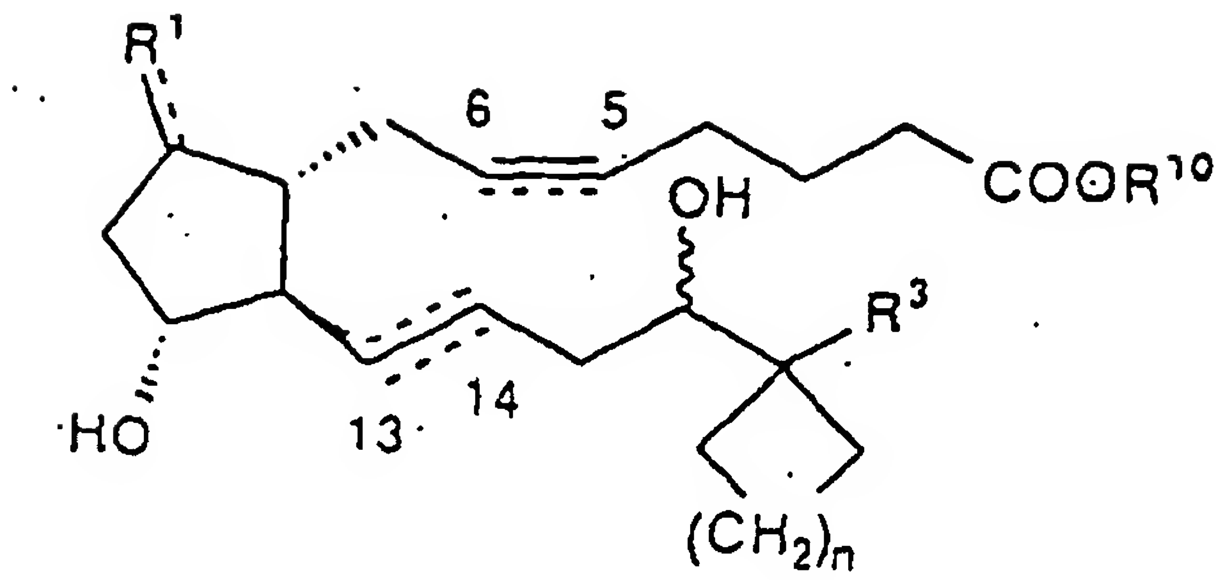
wherein R^{21} is hydrogen atom or hydroxy protecting group which may be eliminated under acidic conditions, and the other symbols are as defined in claim 1 or 9.

13. A process for the preparation of a prodrug compound of formula (IA) as defined in claim 1, which is of formula a (IA-2)



(IA-2)

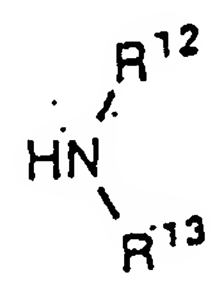
wherein R^{23} is C1-4 alkoxy and the other symbols are as defined in claim 1, which process comprises O-alkylation of a compound of formula (IA-3)



(IA-3)

wherein all the symbols are as defined in claim 1.

14. A process for the preparation of a prodrug compound of formula (IB) as defined in claim 1, which process comprises amidation of a compound of formula (I-1) as defined in claim 8 with a compound of formula (IV)



(IV)

wherein all the symbols are as defined in claim 1.

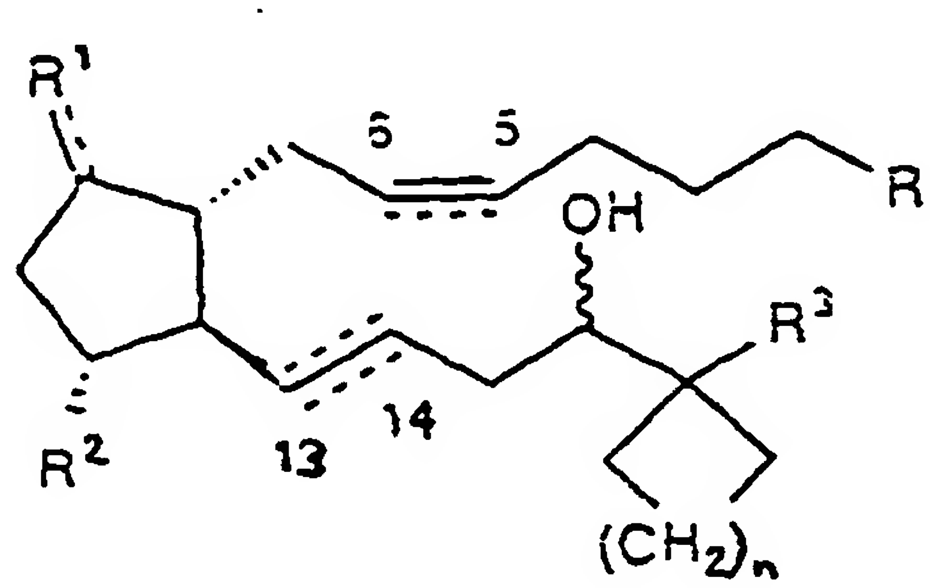
15. A pharmaceutical composition which comprises a compound of formula (I) as defined in claim 1, or a non-toxic salt thereof or cyclodextrin clathrate thereof, or prodrug thereof as defined in claim 1, with a carrier or coating.

16. Use of a compound of formula (I) as defined in claim 1, or a non-toxic salt thereof or cyclodextrin clathrate thereof, or prodrug thereof as defined in claim 1, in the manufacture of a medicament for use as a binder of the EP_2 subtype receptor.

17. Use of a compound of formula (I) as defined in claim 1, or a non-toxic salt thereof or cyclodextrin clathrate thereof, or prodrug thereof as defined in claim 1, in the manufacture of a medicament for the prevention and/or treatment of immunological diseases, asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma.

Patentansprüche

1. ω-Cycloalkyl-prostaglandin-E_2-Derivat der Formel (I)



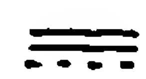
(I)

worin R Carboxy oder Hydroxymethyl ist;
R^1 Oxo, Methylen oder ein Halogenatom ist;
R^2 ein Wasserstoffatom, Hydroxy oder C_{1-4}-Alkoxy ist;
R^3 ein Wasserstoffatom, C_{1-8}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl oder C_{1-8}-Alkyl, C_{2-8}-Alkenyl oder C_{2-8}-Alkinyl, die mit 1-3 Substituenten, ausgewählt aus (1)-(5):

(1) ein Halogenatom,
(2) C_{1-4}-Alkoxy,
(3) C_{3-7}-Cycloalkyl,
(4) Phenyl und
(5) Phenyl, das mit 1-3 Substituenten, ausgewählt aus einem Halogenatom, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Nitro und Trifluormethyl substituiert ist,

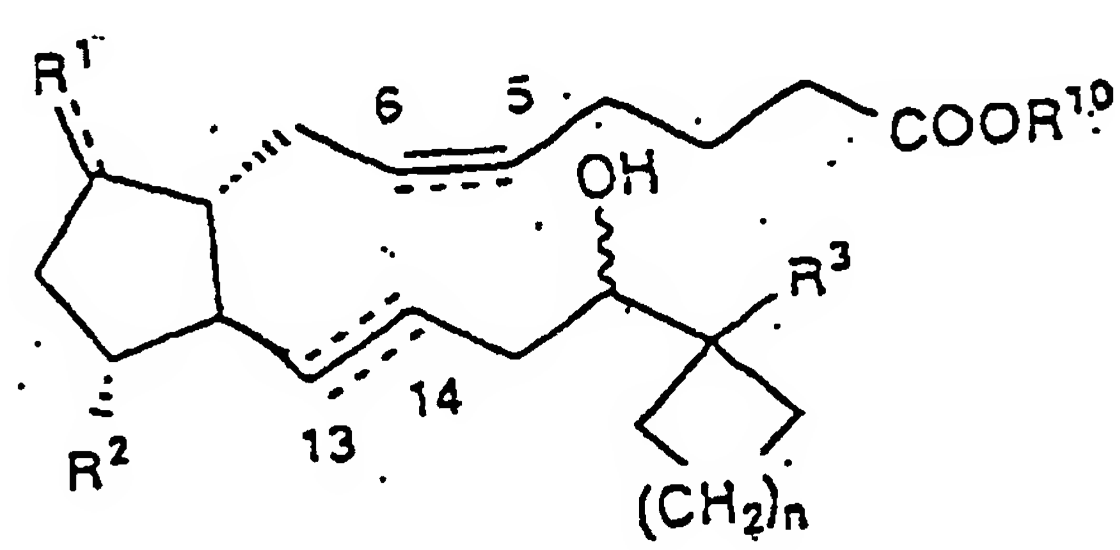
substituiert sind, ist;
n 0-4 ist;

eine Einfachbindung oder Doppelbindung ist;



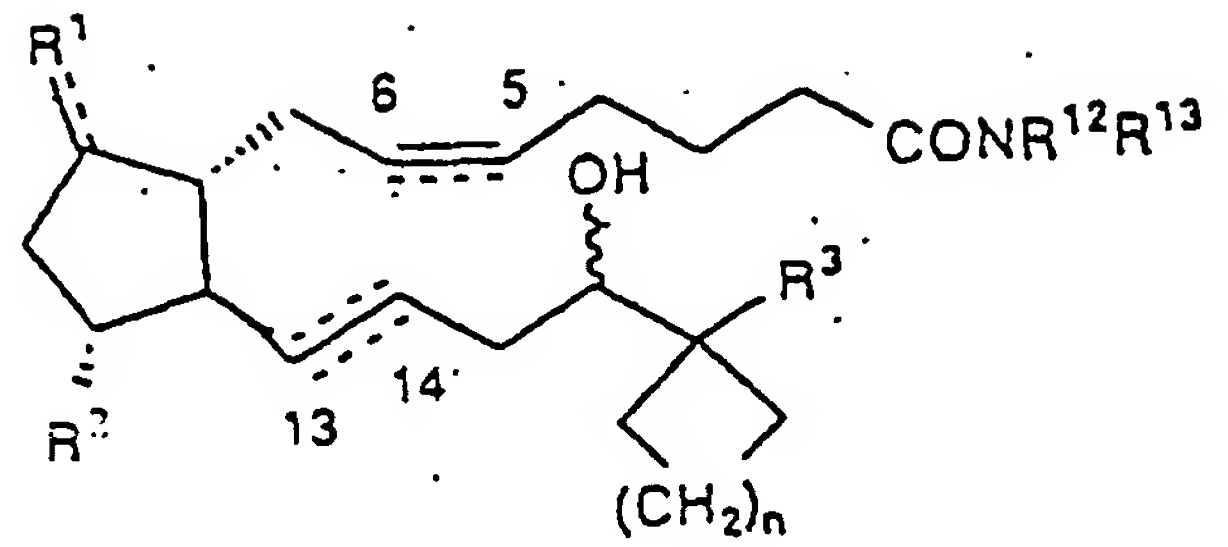
eine Doppelbindung oder Dreifachbindung ist, und

eine Einfachbindung, Doppelbindung oder Dreifachbindung ist;
und worin die Doppelbindung an der 13-14-Position, wenn sie vorhanden ist, in der E-, Z- oder EZ-Gemisch-Form vorhanden ist;
wobei, wenn die 5-6-Position eine Dreifachbindung ist, die 13-14-Position keine Dreifachbindung ist;
oder ein nichttoxisches Salz desselben, ein Cyclodextrinclathrat desselben oder eine Prodrug desselben der Formel (IA)



(IA)

worin R^{10} C_{1-6}-Alkyl ist und die anderen Symbole die obige Bedeutung besitzen, oder der Formel (IB)



(IB)

worin R^{12} und R^{13} jeweils unabhängig voneinander ein Wasserstoffatom oder C_{1-6}-Alkyl sind und die anderen Symbole die obige Bedeutung besitzen.

2. Verbindung gemäß Anspruch 1, worin R Carboxy ist.

3. Verbindung gemäß Anspruch 1, worin R Hydroxymethyl ist.

4. Verbindung gemäß Anspruch 1, nämlich

(1) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5,13-diensäuremethylester,
(2) (5Z,11α,16RS)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5-en-13-insäuremethylester,
(3) (11α,13E)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-13-en-5-insäuremethylester,
(4) (5Z,11α,16RS)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5-ensäuremethylester,
(5) (5Z,11α,13E)-11,16-Dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-diensäuremethylester,
(6) (5Z,11α,13E)-11,16-Dihydroxy-20-ethyl-9-oxo-17,17-propanoprosta-5,13-diensäuremethylester,
(7) (5Z,11α,13E)-20-Chlor-11,16-dihydroxy-9-oxo-17,17-propanoprosta-5,13-diensäuremethylester,
(8) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-18-phenyl-17,17-propano-19,20-dinorprosta-5,13-diensäuremethylester,
(9) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5,13,19-triensäuremethylester,
(10) (5Z,11α,13E)-11,16-Dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-dien-19-insäuremethylester,
(11) (5Z,11α,13E)-17,17-Butano-11,16-dihydroxy-9-oxoprosta-5, 13-diensäuremethylester,
(12) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-17,17-pentanoprosta-5,13-diensäuremethylester,
(13) (5Z,11α,13E)-18-cyclohexyl-11,16-dihydroxy-9-oxo-17,17-propano-19,20-dinorprosta-5, 13-diensäuremethylester,
(14) (5Z,11α,13E) -11,16-Dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-diensäuremethylester,
(15) (5Z,11α,13E)-17,17-Propano-19,20-methano-11,16-dihydroxy-9-oxoprosta-5,13-diensäuremethylester,
(16) (5Z,11α,13E)-17,17-Propano-20,20-methylen-11,16-dihydroxy-9-oxoprosta-5,13-diensäuremethylester,
(17) (5Z,11α,13E)-17,17-Propano-20-methoxy-11,16-dihydroxy-9-oxoprosta-5,13-diensäuremethylester,
(18) (5Z,11α,13E)-17,17-Propano-20-fluor-11,16-dihydroxy-9-oxoprosta-5,13-diensäuremethylester,
(19) (5Z,11α,13E)-17,17- Propano-19-methyl-11,16-dihydroxy-9-oxoprosta-5,13-diensäuremethylester,
(20) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxo-20-norprosta-5,13,18-triensäuremethylester,
(21) (5Z,13E)-17,17-Propano-16-hydroxy-9-oxoprosta-5,13-diensäuremethylester,
(22) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13-diensäuremethylester,
(23) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxo-19-methylprosta-5,13-diensäuremethylester,
(24) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxo-19,20-methanoprosta-5, 13-diensäuremethylester,
(25) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxo-20-norprosta-5,13-diensäuremethylester,
(26) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13,19-triensäuremethylester,
(27) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9,9-methylenprosta-5,13-diensäuremethylester,
(28) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-fluorprosta-5,13-diensäuremethylester,
(29) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-20-norprosta-5,13-diensäuremethylester,
(30) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlorprosta-5,13,19-triensäuremethylester,
(31) (5Z,9β,11α,13E)-17,17-Propano-19,20-methano-11,16-dihydroxy-9-chlorprosta-5,13-diensäuremethylester,
(32) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-19-methylprosta-5,13-diensäuremethylester,

(33) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlorprosta-5,13-diensäuremethylester,
(34) (5Z,9α,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlorprosta-5,13-diensäuremethylester,
(35) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxo-19,20-dinorprosta-5,13-diensäuremethylester,
(36) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxo-18,19,20-trinorprosta-5,13-diensäuremethylester,
(37) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-19,20-dinorprosta-5,13-diensäuremethylester, oder
(38) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-18,19,20-trinorprosta-5,13-diensäuremethylester, in der Form des stärker oder weniger polaren Stereoisomers an der 16-Position oder eines Gemischs derselben.

5. Verbindung gemäß Anspruch 1, nämlich

(1) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxoprosta-5,13-diensäureamid,
in der Form des stärker oder weniger polaren Stereoisomers an der 16-Position oder eines Gemischs derselben.

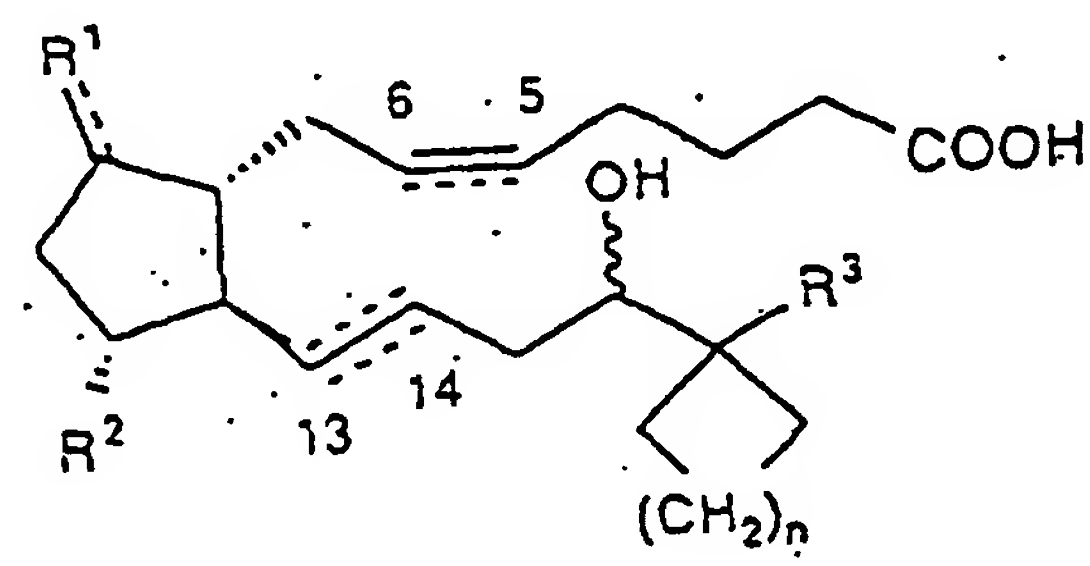
6. Verbindung gemäß Anspruch 2, nämlich

(1) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5,13-diensäure,
(2) (5Z,11α,13E)-11,16-Dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-diensäure,
(3) (5Z,11α,13E)-11,16-Dihydroxy-20-ethyl-9-oxo-17,17-propanoprosta-5,13-diensäure,
(4) (5Z,11α,13E)-20-Chlor-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5,13-diensäure,
(5) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-18-phenyl-17,17-propano-19,20-dinorprosta-5,13-diensäure,
(6) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5,13,19-triensäure,
(7) (5Z,11α,13E)-11,16-Dihydroxy-20-methyl-9-oxo-17,17-propanoprosta-5,13-dien-19-insäure,
(8) (5Z,11α,13E)-17,17-Butano-11,16-dihydroxy-9-oxoprosta-5,13-diensäure,
(9) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-17,17-pentanoprosta-5,13-diensäure,
(10) (5Z,11α,13E)-18-Cyclohexyl-11,16-dihydroxy-9-oxo-17,17-propano-19,20-dinorprosta-5,13-diensäure,
(11) (5Z,11α,13E)-11,16-Dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-diensäure,
(12) (5Z,11α,16RS)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5-ensäure,
(13) (5Z,11α,16RS)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-5-en-13-insäure,
(14) (11α,13E)-11,16-Dihydroxy-9-oxo-17,17-propanoprosta-13-en-5-insäure,
(15) (5Z,11α,13E)-17,17-Propano-19,20-methano-11,16-dihydroxy-9-oxoprosta-5,13-diensäure,
(16) (5Z,11α,13E)-17,17-Propano-20,20-methylen-11,16-dihydroxy-9-oxoprosta-5,13-diensäure,
(17) (5Z,11α,13E)-17,17-Propano-20-methoxy-11,16-dihydroxy-9-oxoprosta-5,13-diensäure,
(18) (5Z,11α,13E)-17,17-Propano-20-fluor-11,16-dihydroxy-9-oxoprosta-5,13-diensäure,
(19) (5Z,11α,13E)-17,17-Propano-19-methyl-11,16-dihydroxy-9-oxoprosta-5,13-diensäure,
(20) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxo-20-norprosta-5,13,18-triensäure,
(21) (5Z,11α,13Z)-17,17-Propano-11,16-dihydroxy-9-oxoprosta-5,13-diensäure,
(22) (5Z,13E)-17,17-Propano-16-hydroxy-9-oxoprosta-5,13-diensäure,
(23) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13-diensäure,
(24) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-19-methyl-9-oxoprosta-5,13-diensäure,
(25) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxo-19,20-methanoprosta-5,13-diensäure,
(26) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxo-20-norprosta-5,13-diensäure,
(27) (5Z,11α,13E)-17,17-Propano-11-methoxy-16-hydroxy-9-oxoprosta-5,13,19-triensäure,
(28) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9,9-methylenprosta-5,13-diensäure,
(29) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-fluorprosta-5,13-diensäure,
(30) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-20-norprosta-5,13-diensäure,
(31) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlorprosta-5,13,19-triensäure,
(32) (5Z,9β,11α,13E)-17,17-Propano-19,20-methano-11,16-dihydroxy-9-chlorprosta-5,13-diensäure,
(33) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-19-methylprosta-5,13-diensäure,
(34) (5Z,9α,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlorprosta-5,13-diensäure,
(35) (5Z,9α,11V,13E)-17,17-Propano-11,16-dihydroxy-9-chlorprosta-5,13-diensäure,
(36) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxo-19,20-dinorprosta-5,13-diensäure,
(37) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxo-18,19,20-trinorprosta-5,13-diensäure,
(38) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-19,20-dinorprosta-5,13-diensäure, oder
(39) (5Z,9β,11α,13E)-17,17-Propano-11,16-dihydroxy-9-chlor-18,19,20-trinorprosta-5,13-diensäure,
in der Form des stärker oder weniger polaren Stereoisomers an der 16-Position oder eines Gemischs dersel-

ben.

7. Verbindung gemäß Anspruch 3, nämlich (1) (5Z,11α,13E)-17,17-Propano-11,16-dihydroxy-9-oxoprosta-5,13-dien-1-ol, in der Form des stärker oder weniger polaren Stereoisomers an der 16-Position oder eines Gemischs derselben.

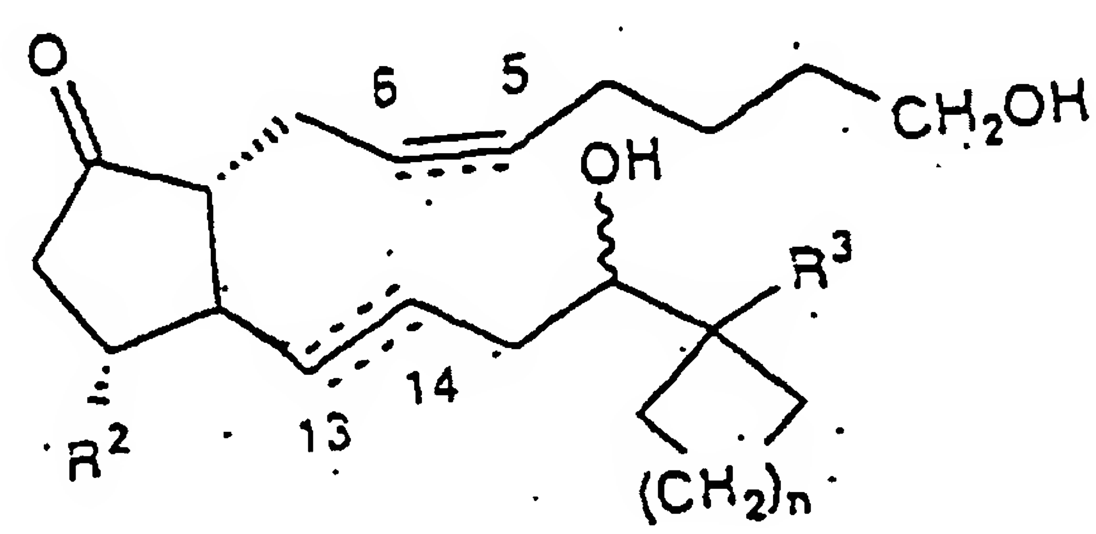
8. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1, die die Formel (I-1) aufweist,



(I-1)

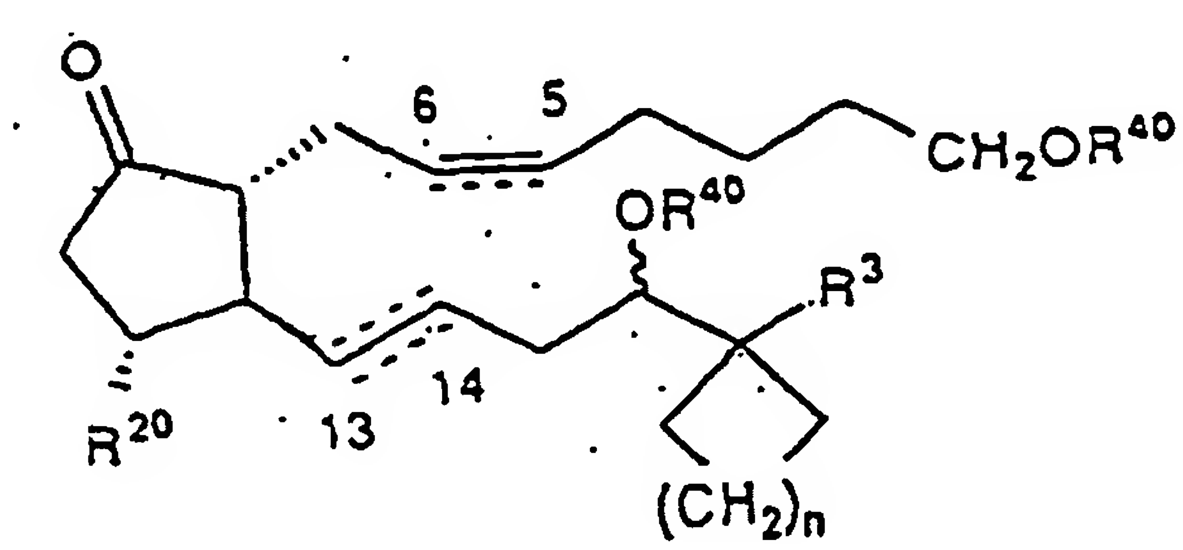
worin alle Symbole wie in Anspruch 1 definiert sind, wobei das Verfahren eine Hydrolyse einer Verbindung der Formel (IA) gemäß der Definition in Anspruch 1 unter Verwendung eines Enzyms oder unter alkalischen Bedingungen umfasst.

9. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1, die die Formel (I-2A) aufweist,



(I-2A)

worin alle Symbole wie in Anspruch 1 definiert sind,
wobei das Verfahren die Entfernung der Schutzgruppe(n) einer Verbindung der Formel (IIA)

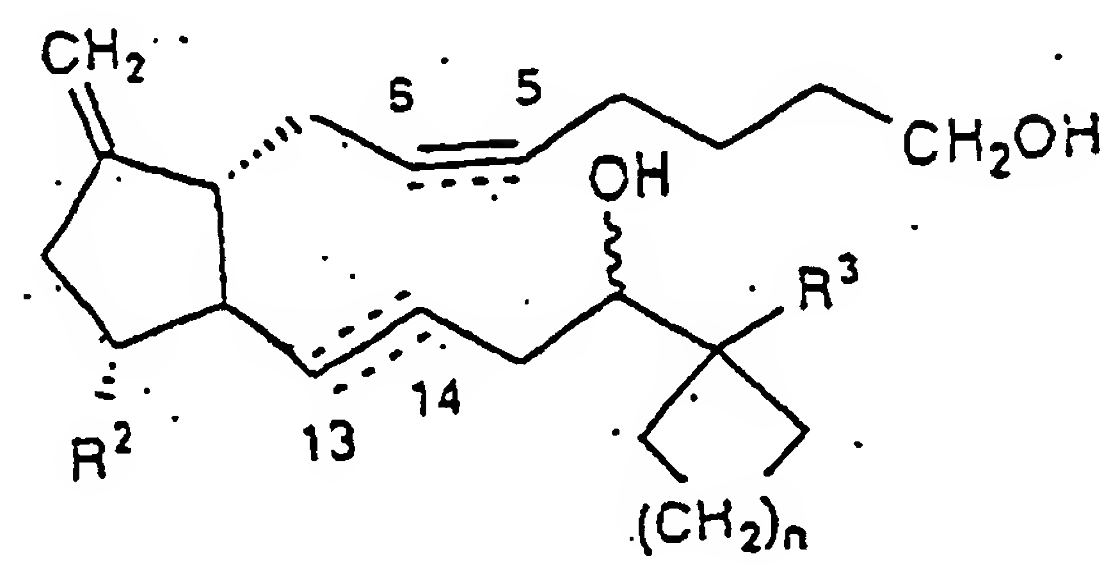


(IIA)

worin R^{20} ein Wasserstoffatom, eine unter sauren Bedingungen entfernbare Hydroxyschutzgruppe oder C_{1-4}-Alkoxy ist, R^{40} eine unter sauren Bedingungen entfernbare Hydroxyschutzgruppe ist und die anderen Symbole wie

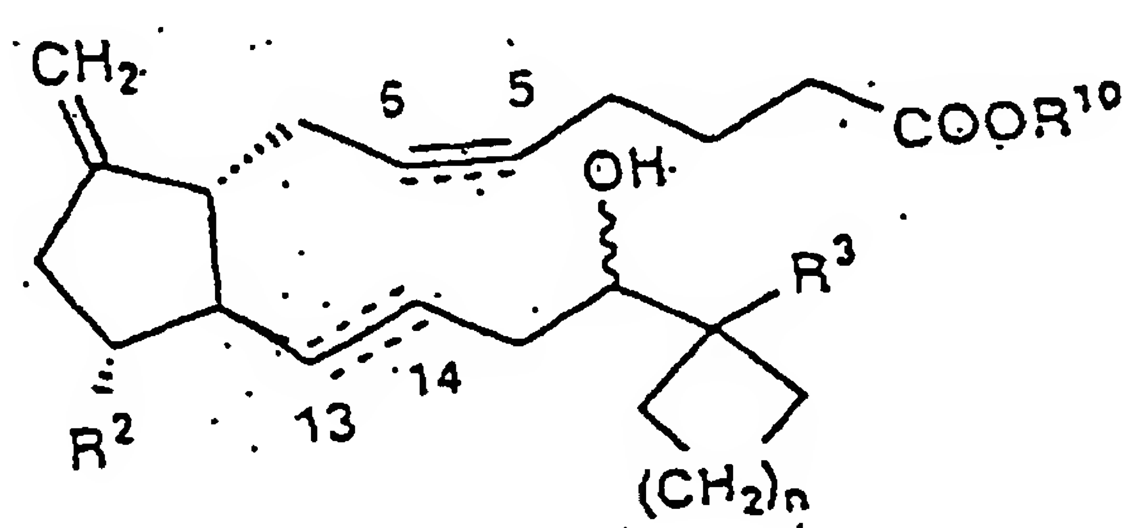
in Anspruch 1 definiert sind,
unter sauren Bedingungen umfasst.

10. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1, die die Formel (I-2B) aufweist,



(I-2B)

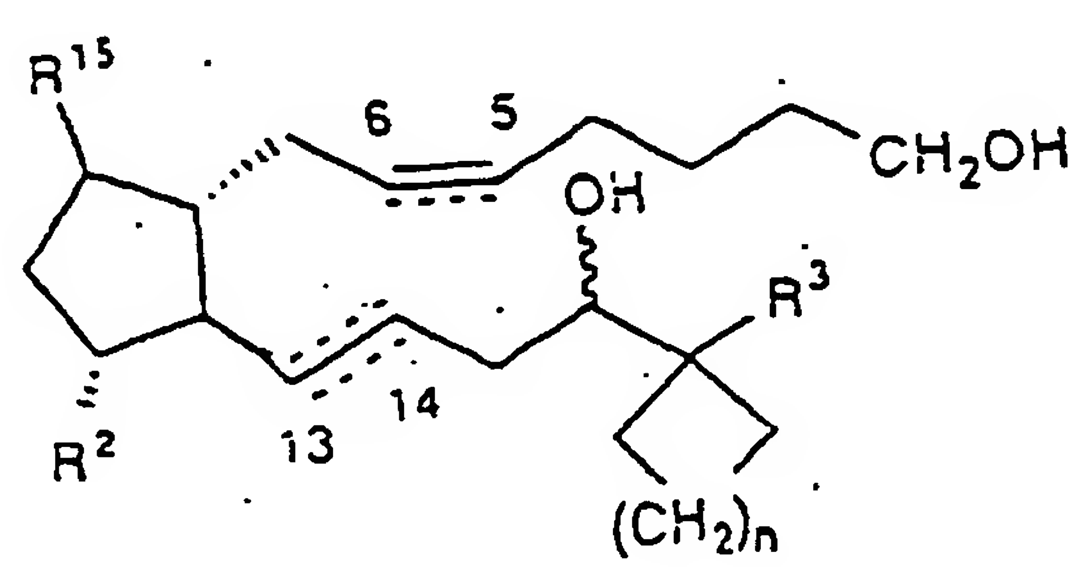
worin alle Symbole wie in Anspruch 1 definiert sind,
wobei das Verfahren die Reduktion einer Verbindung der Formel (IA-4)



(IA-4)

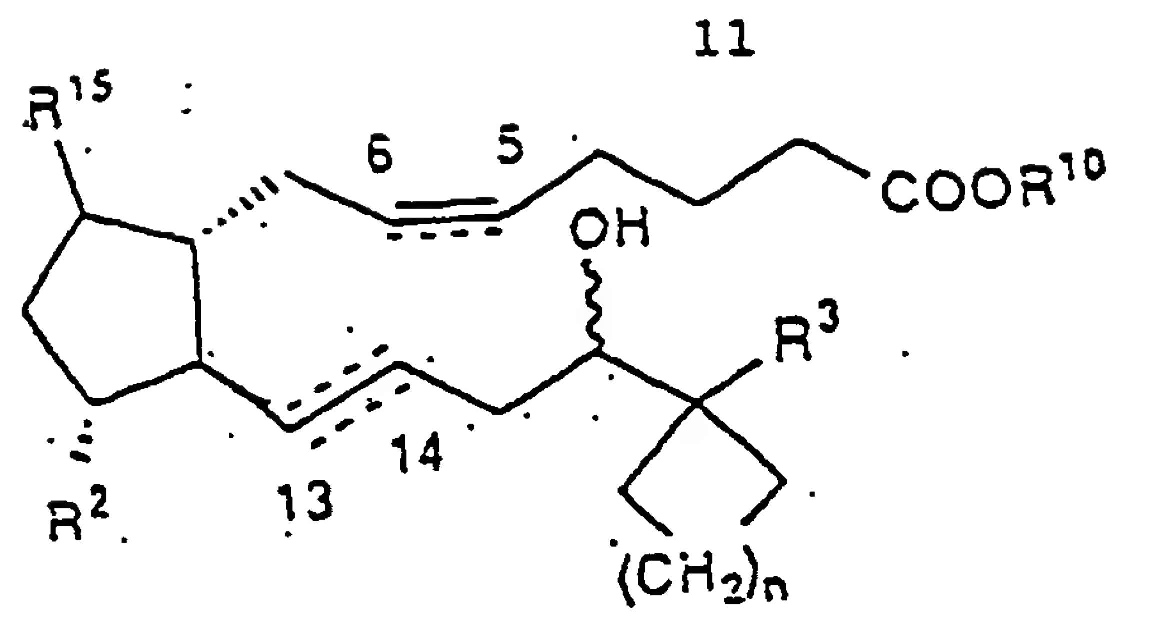
worin alle Symbole wie in Anspruch 1 definiert sind, umfasst.

11. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1, die die Formel (I-2C) aufweist,



(I-2C)

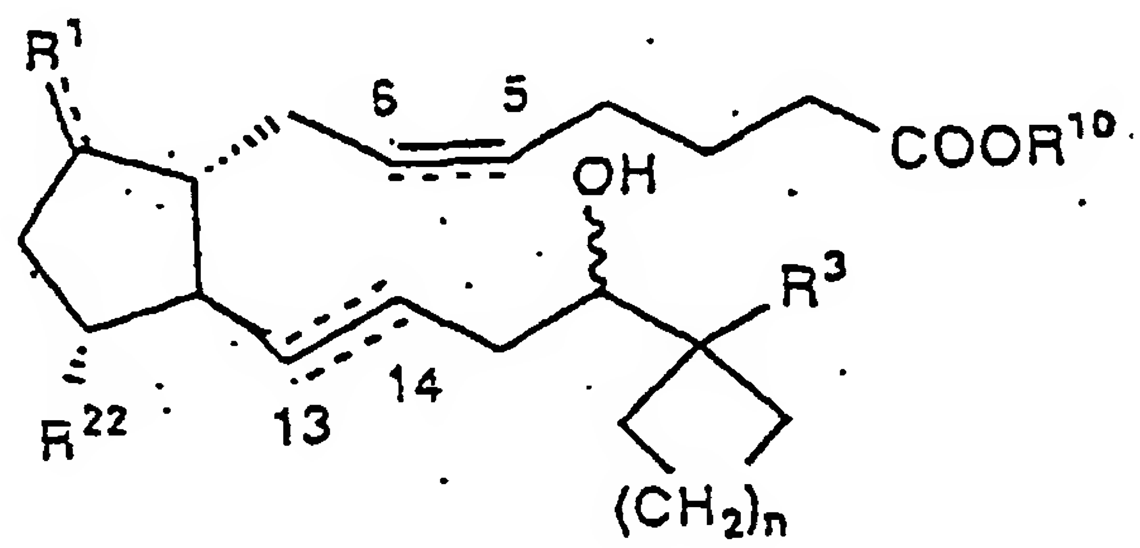
worin R^{15} ein Halogenatom ist und die anderen Symbole wie in Anspruch 1 definiert sind, wobei das Verfahren die Reduktion einer Verbindung der Formel (IA-5)



(IA-5)

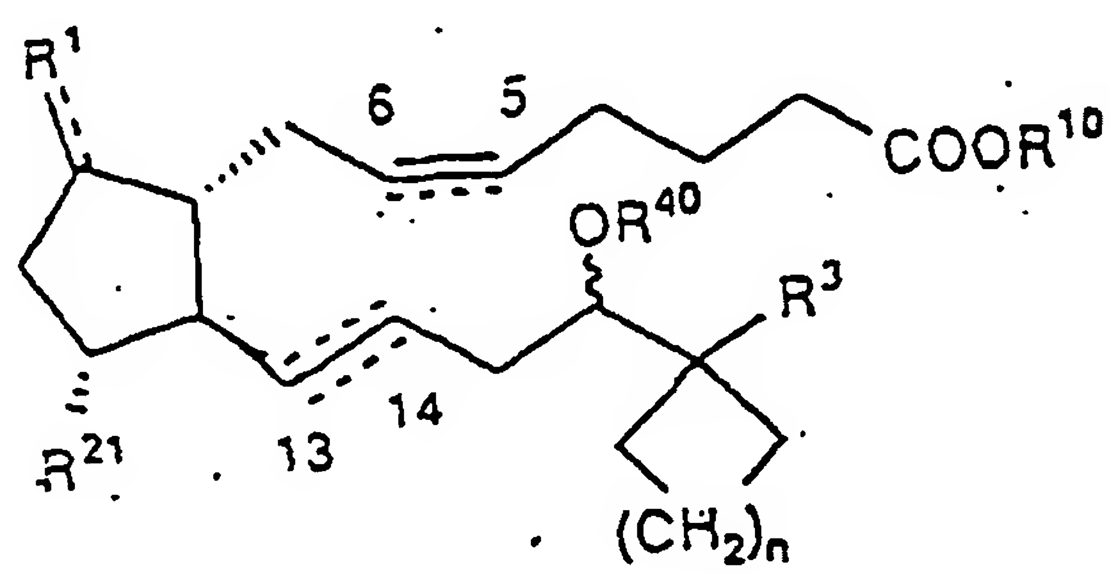
worin R^{15} ein Halogenatom ist und die anderen Symbole wie in Anspruch 1 definiert sind, umfasst.

12. Verfahren zur Herstellung einer Prodrugverbindung der Formel (IA) gemäß der Definition in Anspruch 1, die die Formel (IA-1) aufweist,



(IA-1)

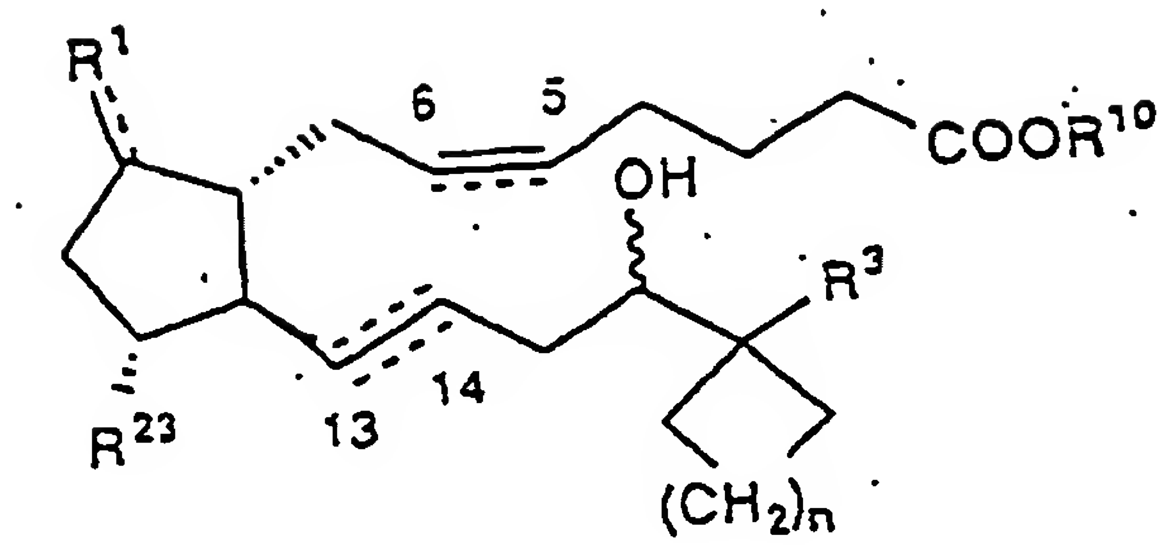
worin R^{22} ein Wasserstoffatom oder Hydroxy ist und die anderen Symbole wie in Anspruch 1 definiert sind, wobei das Verfahren die Hydrolyse einer Verbindung der Formel (III)



(III).

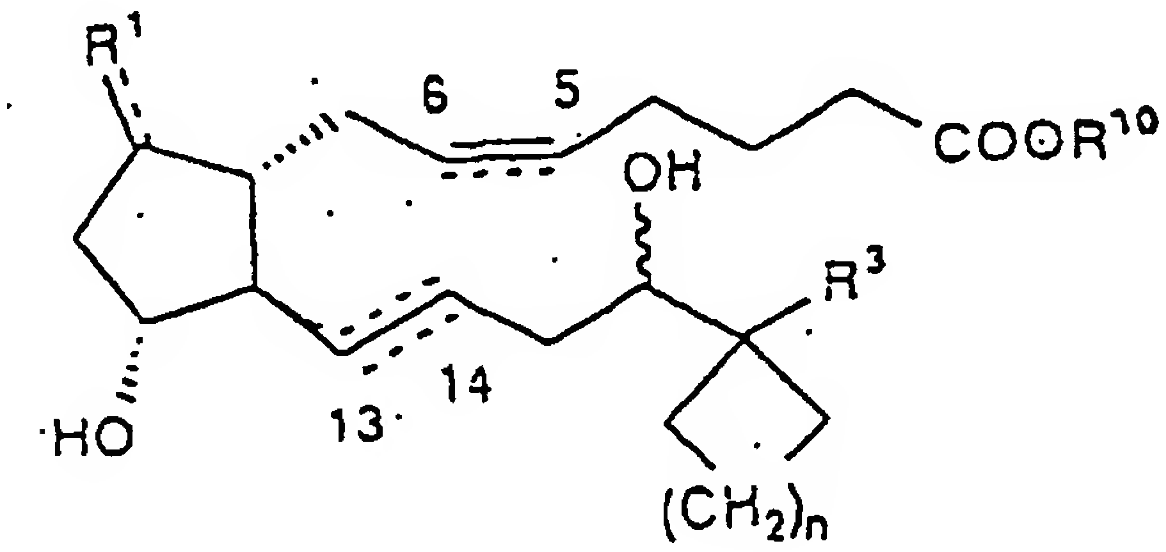
worin R^{21} ein Wasserstoffatom oder eine unter sauren Bedingungen entfernbare Hydroxyschutzgruppe ist und die anderen Symbole wie in den Ansprüchen 1 oder 9 definiert sind, unter sauren Bedingungen umfasst.

13. Verfahren zur Herstellung einer Prodrugverbindung der Formel (IA) gemäß der Definition in Anspruch 1, die die Formel (IA-2) aufweist,



(IA-2)

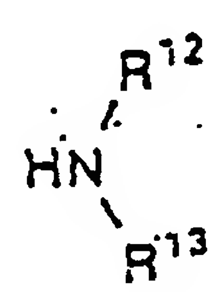
worin R^{23} C_{1-4}-Alkoxy ist und die anderen Symbole wie in Anspruch 1 definiert sind, wobei das Verfahren die O-Alkylierung einer Verbindung der Formel (IA-3)



(IA-3)

worin alle Symbole wie in Anspruch 1 definiert sind, umfasst.

14. Verfahren zur Herstellung einer Prodrugverbindung der Formel (IB) gemäß der Definition in Anspruch 1, wobei das Verfahren die Amidierung einer Verbindung der Formel (I-1) gemäß der Definition in Anspruch 1 mit einer Verbindung der Formel (IV)



(IV)

worin alle Symbole wie in Anspruch 1 definiert sind, umfasst.

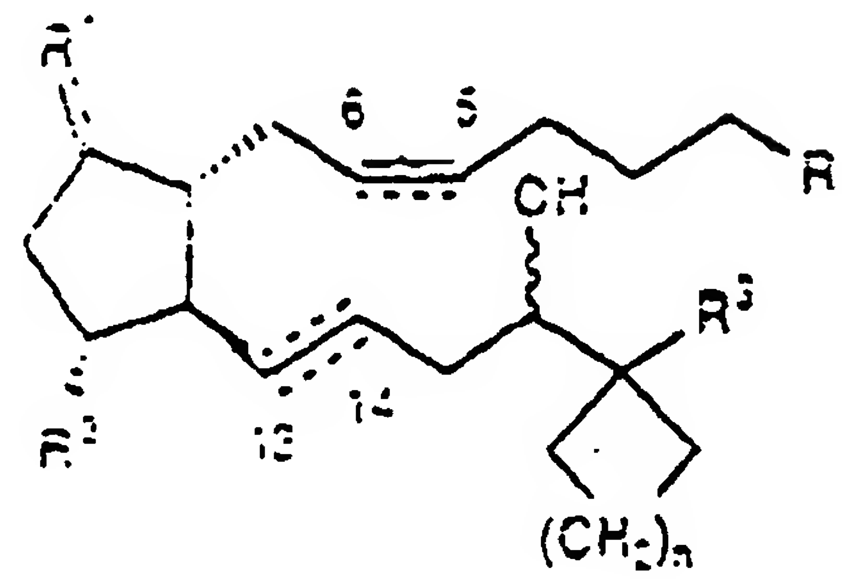
15. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) gemäß der Definition in Anspruch 1 oder ein nichttoxisches Salz derselben oder ein Cyclodextrinclathrat derselben oder eine Prodrug derselben gemäß der Definition in Anspruch 1 mit einem Träger oder Überzug umfasst.

16. Verwendung einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1 oder eines nichttoxischen Salzes derselben oder eines Cyclodextrinclathrats derselben oder einer Prodrug derselben gemäß der Definition in Anspruch 1 bei der Herstellung eines Medikaments zur Verwendung als Bindemittel des EP_2-Subtyp-Rezeptors.

17. Verwendung einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1 oder eines nichttoxischen Salzes derselben oder eines Cyclodextrinclathrats derselben oder einer Prodrug derselben gemäß der Definition in Anspruch 1 bei der Herstellung eines Medikaments zur Prävention und/oder Behandlung von immunologischen Erkrankungen, Asthma, anomaler Knochenbildung, Absterben neuronaler Zellen, Leberschädigung, Fehlgeburt, Frühgeburt oder Glaukomretinoneuropathie.

Revendications

1. Dérivé oméga-cycloalkyle-prostaglandine E_2 de la formule (I)



(I)

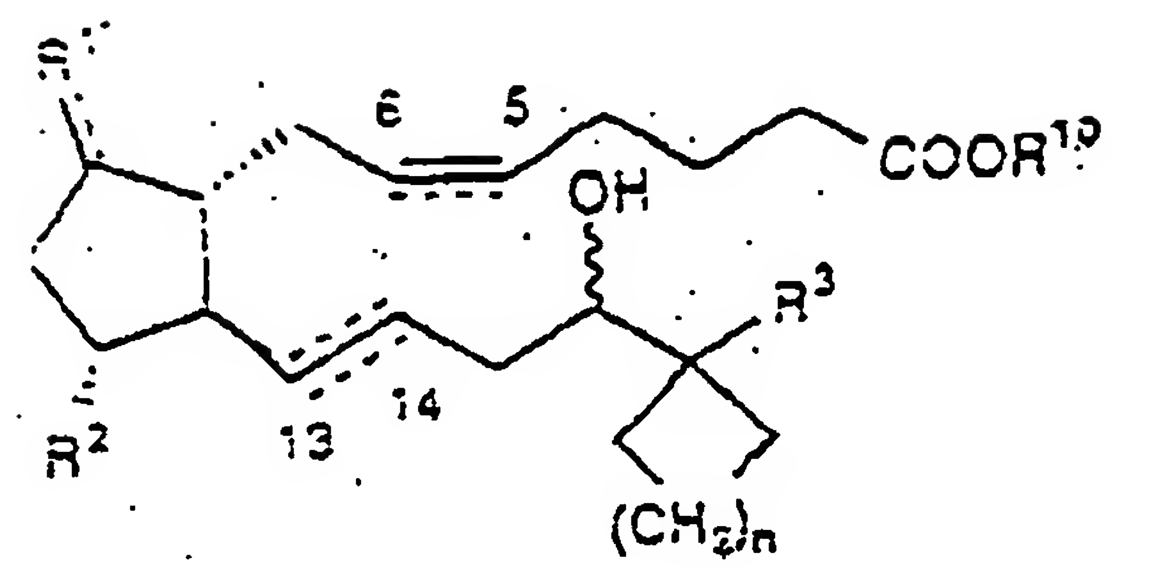
dans laquelle R est un carboxy ou un hydroxyméthyle ;
R^1 est un oxo, un méthylène ou un atome d'halogène ;
R^2 est un atome d'hydrogène, un hydroxy ou un alkoxy de C1 à 4 ;
R^2 est un atome d'hydrogène, un alkyle de C1 à 8, un alcényle de C2 à 8, un alkynyl de C2 à 8 ou un alkyle de C1 à 8, ou un alcényle de C2 à 8 ou un alkynyl de C2 à 8, substitué par 1 à 3 substituants sélectionnés dans (1) à (5) :

(1) atome d'halogène,
(2) alkoxy de C1 à 4,
(3) cycloalkyle de C3 à 7,
(4) phényle, et
(5) phényle substitué par 1 à 3 substituants sélectionnés dans un atome d'halogène, un alkyle de C1 à 4, un alkoxy de C1 à 4, un nitro et un trifluorométhyle ;

n est de 0 à 4 ;
est une liaison simple ou une liaison double ;

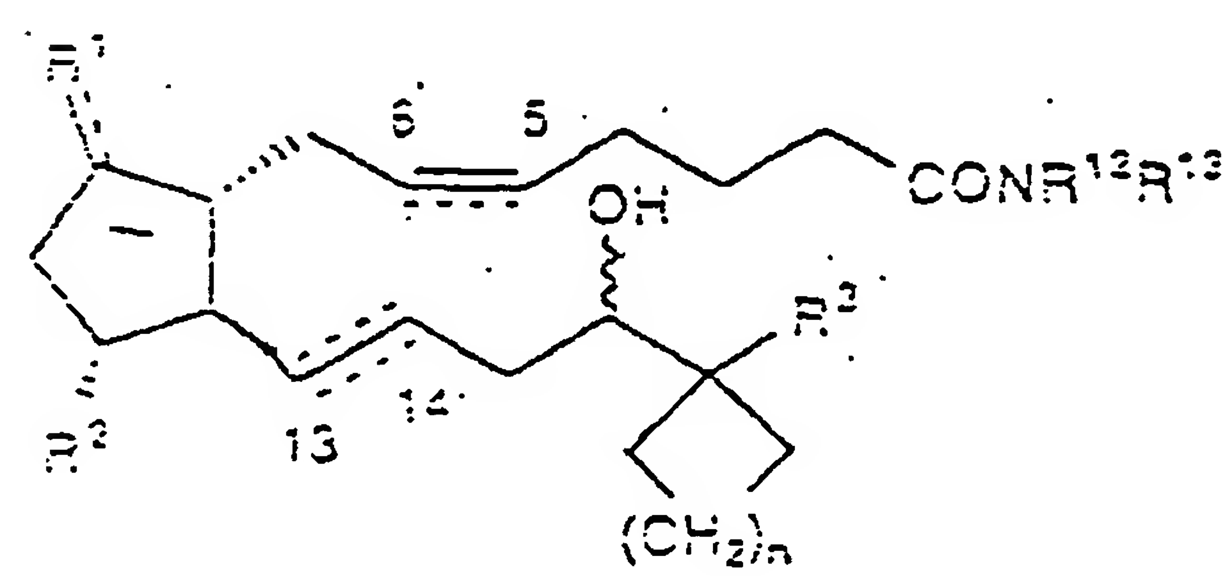
est une liaison double ou une liaison triple ; et

est une liaison simple, une liaison double ou une liaison triple ;
et dans laquelle la liaison double en position 13 à 14, lorsqu'elle est présente, est sous forme de mélange E, Z, ou EZ ;
à la condition expresse que lorsque la position 5 à 6 est une liaison triple, la position 13 à 14 ne soit pas une liaison triple ;
ou un sel non toxique de ceux-ci, un clathrate de cyclodextrine de ceux-ci, ou un promédicament de ceux-ci de formule (IA)



(IA)

dans laquelle R^{10} est un alkyle de C1 à 6 et les autres symboles sont tels que définis ci-dessus, ou de formule (IB)



(IB)

dans laquelle R^{12} et R^{13} chacun, indépendamment, est un atome d'hydrogène ou un alkyle de C1 à 6 et les autres symboles sont tels que définis ci-dessus.

2. Composé selon la revendication 1, dans lequel R est un carboxy.

3. Composé selon la revendication 1, dans lequel R est un hydroxyméthyle.

4. Composé selon la revendication 1, qui est

(1) (5Z,11α,13E) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5,13-dienotate de méthyle,
(2) (5Z,11α,16RS) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5-ene 13-ynoic acid . methylester,
(3) (11α,13E) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 13-ene 15-ynoic acid . methylester,
(4) (5Z,11α,16RS) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5-enoic acid . methylester,
(5) (5Z,11α,13E) 11,16-dihydroxy 20-méthyle 9-oxo 17,17-propanoprosta 5,13-dienotate de méthyle,
(6) (5Z,11α,13E) 11,16-dihydroxy 20-éthyle 9-oxo 17,17-propanoprosta 5,13-dienotate de méthyle,
(7) (5Z,11α,13E) 20-chloro 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5,13-dienotate de méthyle,
(8) (5Z, 11α, 13E) 11,16-dinydroxy 9-oxo 18-phényle 17,17-propano 19,20-dinorprosta 5,13-dienotate de méthyle,
(9) (5Z,11α,13E) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5,13,19-trienotate de méthyle,
(10) (5Z,11α,13E) 11,16-dihydroxy 20-méthyle 9-oxo 17,17-propanoprosta 5,13-diene 19-ynoic acid. methylesther,
(11) (5Z,11α,13E) 17,17-butano 11,16-dihydroxy 9-oxoprosta 5,13-dienotate de méthyle,
(12) (5Z,11α,13E) 11,16-dihydroxy 9-oxo 17,17-pentanoprosta 5,13 dienotate de méthyle,
(13) (5Z,11α,13E) 16-cyclohexyl 11,16-dihydroxy 9-oxo 17,17-propano 19,20-dinorprosta 5,13-dienotate de méthyle,
(14) (5Z,11α,13E) 11,16-dihydroxy 9-oxo-17,17-propano 20-norprosta 5,13-dienotate de méthyle,
(15) (5Z,11α,13E) 17,17-propano 19,20-méthano 11,16-dihydroxy 9-oxoprosta 5,13-dienotate de méthyle,
(16) (5Z,11α,13E) 17,17-propano 20,20-méthylène 11,16-dihydroxy 9-oxoprosta 5,13-dienotate de méthyle,
(17) (5Z,11α,13E) 17,17-propano 20-méthoxy 11,16-dihydroxy 9-oxoprosta 5,13-dienotate de méthyle,
(18) (5Z,11α,13E) 17,17-propano 20-fluoro 11,16-dihydroxy 9-oxoprosta 5,13-dienotate de méthyle,

(19) (5Z,11α,13E) 17,17-propano 19-méthyle 11,16-dihydroxy 9-oxoprosta 5,13-dienotate de méthyle,
(20) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxo 20-norprosta 5,13,18-trienotate de méthyle,
(21) (5Z,13E) 17,17-propano 16-hydroxy 9-oxoprosta 5,13-dienotate de méthyle,
(22) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxoprosta 5,13-dienotate de méthyle,
(23) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxo 19-méthylprosta 5,13-dienotate de méthyle,
(24) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxo 19,20-méthanoprosta 5,13-dienotate de méthyle,
(25) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxo 20 norprosta 5,13-dienotate de méthyle,
(26) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxoprosta 5,13,19-trienotate de méthyle,
(27) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9,9-méthylèneprosta 5,13-dienotate de méthyle,
(28) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-fluoro-prosta 5,13-dienotate de méthyle,
(29) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 20-norprosta 5,13-dienotate de méthyle,
(30) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloroprosta 5,13,19-trienotate de méthyle,
(31) (5Z,9β,11α,13E) 17,17-propano 19,20-méthano 11,16-dihydroxy 9-chloroprosta 5,13-dienotate de méthyle,
(32) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 19-méthyleprosta 5,13-dienotate de méthyle,
(33) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloroprosta 5,13-dienotate de méthyle
(34) (5Z,9α,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloroprosta 5,13-dienotate de méthyle
(35) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxo 19,20-dinorprosta 5,13-dienotate de méthyle,
(36) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxo 18,19,20-trinorprosta 5,13-dienotate de méthyle,
(37) (5Z,9β,11 α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 19,20-dinorprosta 5,13-dienotate de méthyle, ou
(38) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 18,19,20-trinorprosta 5,13-dienotate de méthyle,
sous forme du stéréo-isomère plus ou moins polaire en position 16 ou d'un mélange de ceux-ci.

5. Composé selon la revendication 1, qui est

(1) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxoprosta 5,13-amide d'acide dienoïque,
sous forme du stéréo-isomère plus ou moins polaire en position 16 ou d'un mélange de ceux-ci.

6. Composé selon la revendication 2, qui est

(1) (5Z,11α,13E) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5,13-acide dienoïque,
(2) (5Z,11α,13E) 11,16-dihydroxy 20-méthyle 9-oxo 17,17-propanoprosta 5,13-acide dienoïque,
(3) (5Z,11α,13E) 11,16-dihydroxy-20-éthyle 9-oxo17,17-propanoprosta-5,13-acide dienoïque,
(4) (5Z,11α,13E) 20-chloro 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5,13-acide dienoïque,
(5) (5Z,11α,13E) 11,16-dihydroxy 9-oxo 16-phényle 17,17-propano 5,20-norprosta 5,13-acide dienoïque,
(6) (5Z,11α,13E) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5,13,19-acide trienoïque,
(7) (5Z,11α,13E) 11,16-dihydroxy 20-méthyle 9-oxo 17,17-propanoprosta 5,13-diene 19-ynoic acid,
(8) (5Z,11α,13E) 17,17-butano 11,16-dihydroxy 9-oxoprosta 5,17-propanoprosta 5,13-acide dienoïque,
(9) (5Z,11α,13E) 11,16-dihydroxy 9-oxo 17,17-pentanoprosta 5,13-acide dienoïque,
(10) (5Z,11α,13E) 18-cyclohexyl 11,16-dihydroxy 9-oxo 17,17-propano 19,20-dinorprosta 5,13-acide dienoïque,
(11) (5Z, 11α, 13E) 11,16-dihydroxy 9-oxo 17,17-propano 20-dinorprosta 5,13-acide dienoïque,
(12) (5Z, 11α, 16RS) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5-acide enoïque,
(13) (5Z,11α,16RS) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 5-ene 13-ynoic acide,
(14) (11α, 13E) 11,16-dihydroxy 9-oxo 17,17-propanoprosta 13-ene 5-ynoic acide,
(15) (5Z,11α,13E) 17,17-propano 19,20-méthano 11,16-dihydroxy 9-oxoprosta 5,13-acide dienoïque,
(16) (5Z,11α,13E) 17,17-propano 20,20-méthylène 11,16-dihydroxy 9-oxoprosta 5,13-acide dienoïque,
(17) (5Z,11α,13E) 17,17-propano 20-méthoxy 11,16-dihydroxy 9-oxoprosta 5,13-acide dienoïque,
(18) (5Z,11α,13E) 17,17-propano 20-fluoro 11,16-dihydroxy 9-oxoprosta 5,13-acide dienoïque,
(19) (5Z,11α,13E) 17,17-propano 19-méthyle 11,16-dihydroxy 9-oxoprosta 5,13-acide dienoïque,
(20) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxo 20-norprosta 5,13-acide dienoïque,
(21) (5Z,11α,13Z) 17,17-propano 11,16-dihydroxy 9-oxoprosta 5,13-acide dienoïque,
(22) (5Z,13E) 17,17-propano 16-hydroxy 9-oxoprosta 5,13-acide dienoique,
(23) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxoprosta 5,13-acide dienoïque,
(24) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 19-mérhyle 9-oxoprosta 5,13-acide dienoique,

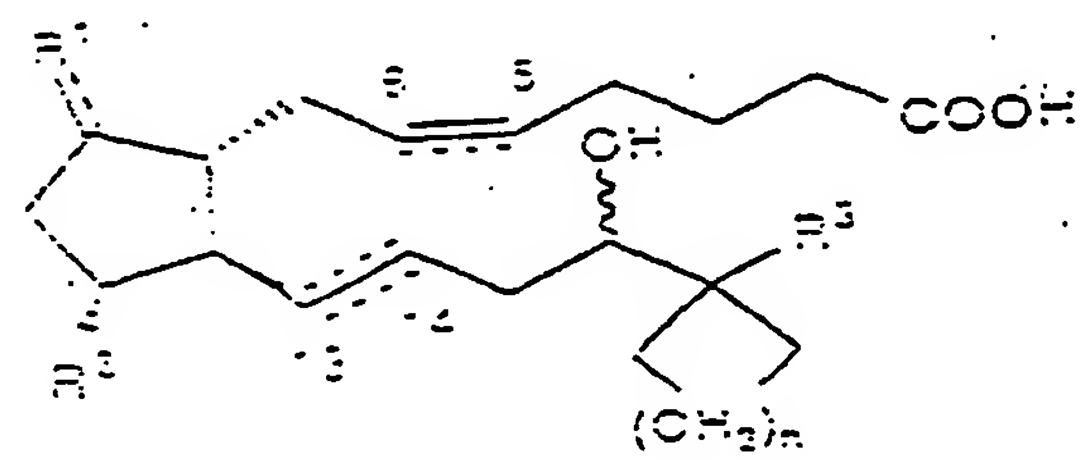
(25) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxo 19,20 méthahoprosta 5,13-acide dienoïque,
(26) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxo 20-norprosta 5,13-acide dienoïque,
(27) (5Z,11α,13E) 17,17-propano 11-méthoxy 16-hydroxy 9-oxoprosta 5,13,19-acide trienoïque,
(28) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy-9,9-méthylèneprosta 5,13-acide dienoïque,
(29) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9,9-fluoro-prosta 5,13-acide dienoïque,
(30) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 20-norprosta 5,13-acide dienoïque,
(31) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloroprosta 5,13,19-trienoic acid,
(32) (5Z,9β,11α,13E) 17,17-propano 19,20-méthano 11,16-dihydroxy 9-chloroprosta 5,13-acide dienoïque,
(33) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 19-méthyleprosta 5,13-acide dienoïque
(34) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloroprosta 5,13-acide dienoïque
(35) (5Z,9β,11V,13E) 17,17-propano 11,16-dihydroxy 9-chloro-prosta 5,13-acide dienoïque
(36) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxo 19,20 dinorprosta 5,13 acide dienoïque
(37) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxo 18,19,20-trinorprosta 5,13-acide dienoïque
(38) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 19,20-dinorprosta 5,13-acide dienoïque, ou
(39) (5Z,9β,11α,13E) 17,17-propano 11,16-dihydroxy 9-chloro 18,19,20-trinorprosta 5,13-acide dienoïque

sous forme du stéréo-isomère plus ou moins polaire en position 16 ou d'un mélange de ceux-ci.

7. Composé selon la revendication 3, qui est

(1) (5Z,11α,13E) 17,17-propano 11,16-dihydroxy 9-oxoprosta 5,13-diene 1-ol,
sous forme du stéréo-isomère plus ou moins polaire en position 16 ou d'un mélange de ceux-ci.

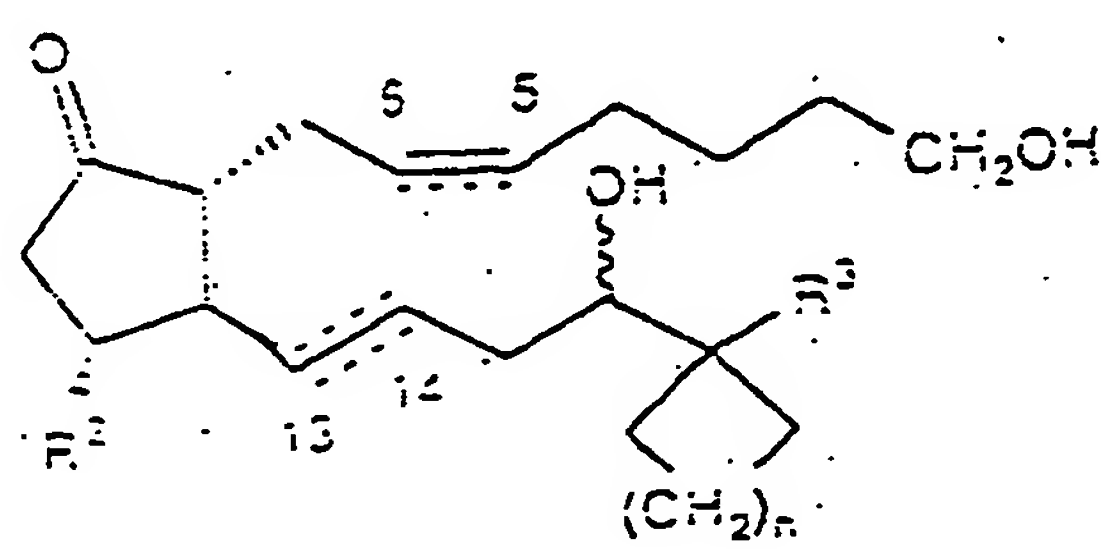
8. Procédé pour la préparation d'un composé de la formule (I) tel que défini dans la revendication 1, qui est de formule (I-1)



(I-1)

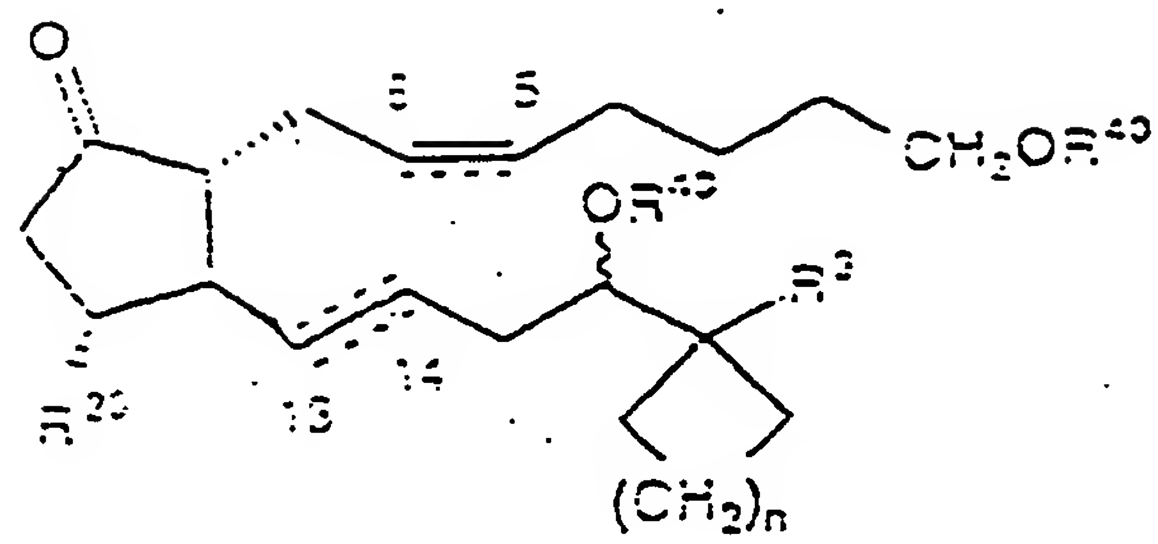
dans laquelle tous les symboles sont tels que définis dans la revendication 1, lequel procédé comprend une hydrolyse enzymatique ou une hydrolyse en milieu alcalin d'un composé de la formule (IA) tel que défini dans la revendication 1.

9. Procédé pour la préparation d'un composé de la formule (I) tel que défini dans la revendication 1, qui est de formule (I-2A)



(I-2A)

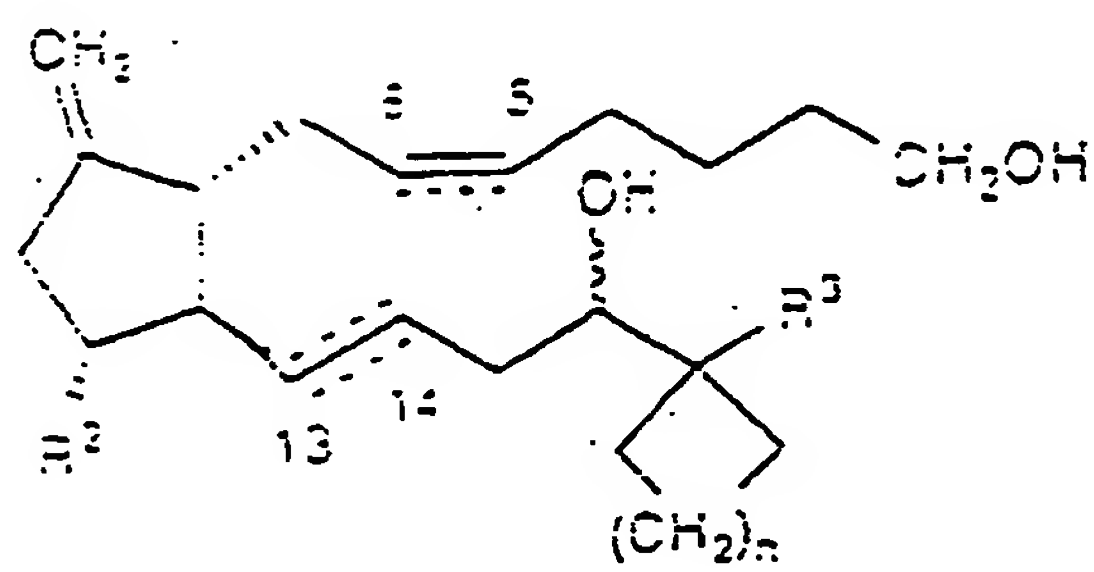
dans laquelle tous les symboles sont tels que définis dans la revendication 1, lequel procédé comprend une élimination en milieu acide du ou des groupes protecteurs d'un composé de la formule (IIA)



(IIA)

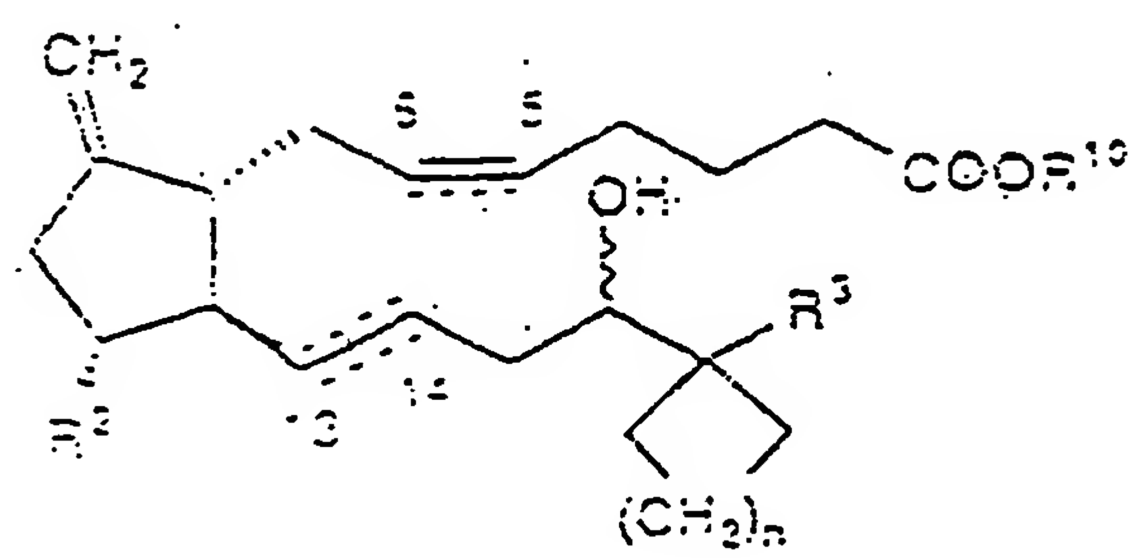
dans laquelle R^{20} est un atome d'hydrogène, un groupe protecteur hydroxy qui peut être éliminé en milieu acide ou un alkoxy de C1 à 4, R^{40} est un groupe protecteur hydroxy qui peut être éliminé en milieu acide, et les autres symboles sont tels que définis dans la revendication 1.

10. Procédé pour la préparation d'un composé de la formule (I) tel que défini dans la revendication 1, qui est de formule (I-2B)



(I-2B)

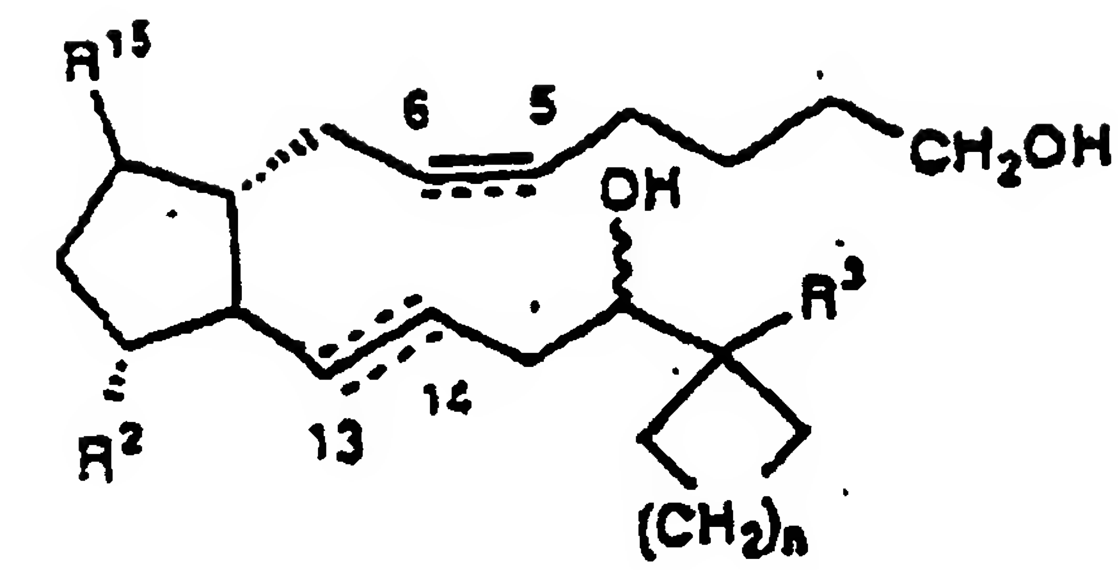
dans laquelle tous les symboles sont tels que définis dans la revendication 1, lequel procédé comprend une réduction d'un composé de la formule (IA-4)



(IA-4)

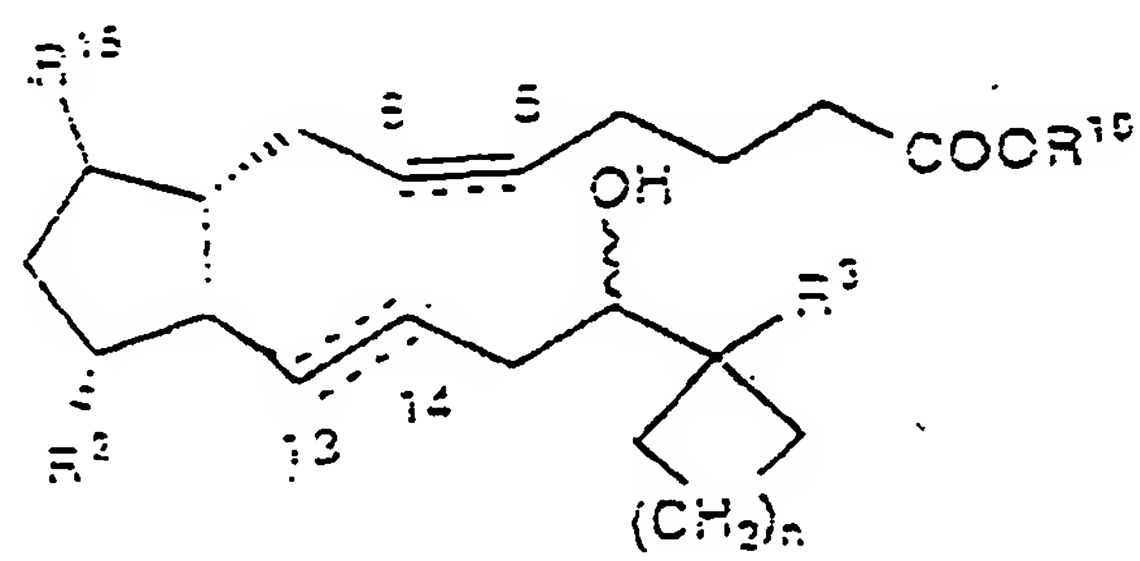
dans laquelle tous les symboles sont tels que définis dans la revendication 1.

11. Procédé pour la préparation d'un composé de la formule (I) tel que défini dans la revendication 1, qui est de formule (I-2C)



(I-2C)

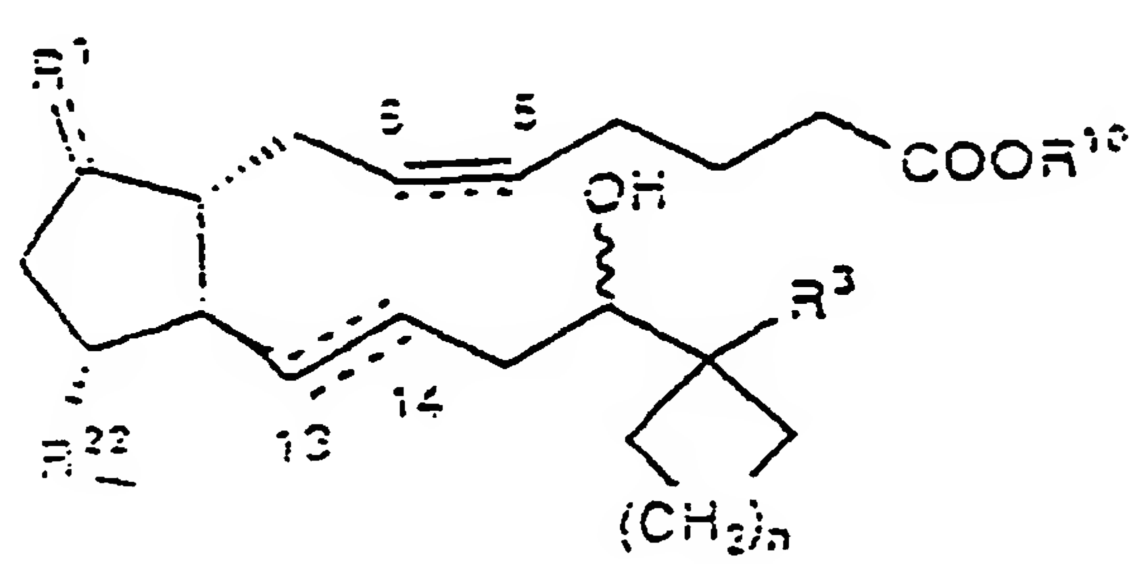
dans laquelle R^{15} est un atome d'halogène et les autres symboles sont tels que définis dans la revendication 1, lequel procédé comprend une réduction d'un composé de la formule (IA-5)



(IA-5)

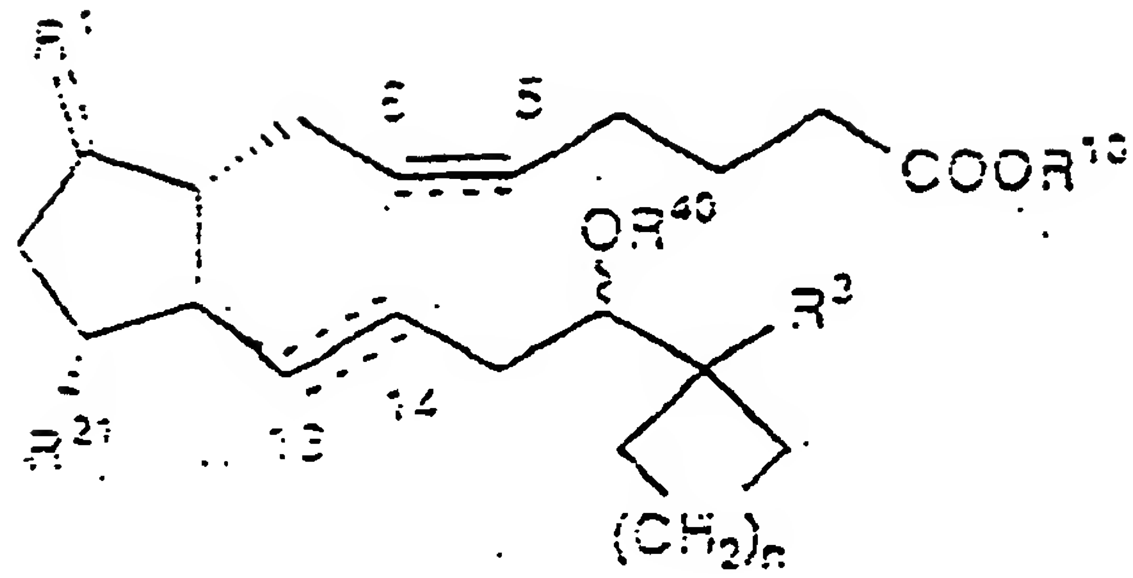
dans laquelle R^{15} est un atome d'halogène, et les autres symboles sont tels que définis dans la revendication 1.

12. Procédé pour la préparation d'un composé promédicamenteux de la formule (IA) tel que défini dans la revendication 1, qui est de formule (IA-1)



(IA-1)

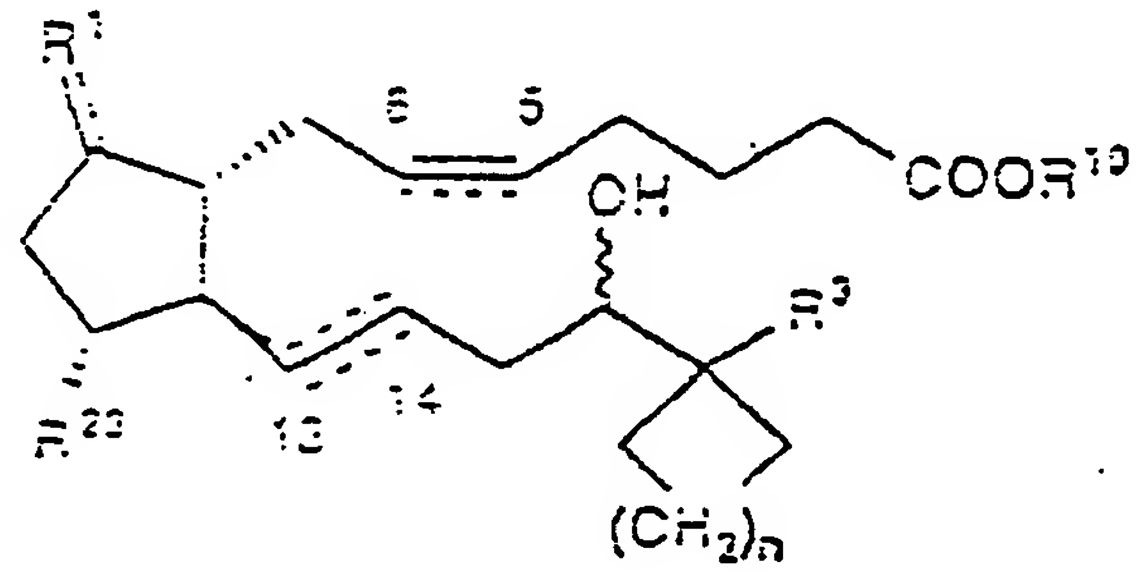
dans laquelle R^{22} est un atome d'hydrogène ou un hydroxy, et les autres symboles sont tels que définis dans la revendication 1, lequel procédé comprend une hydrolyse en milieu acide d'un composé de la formule (III)



(III)

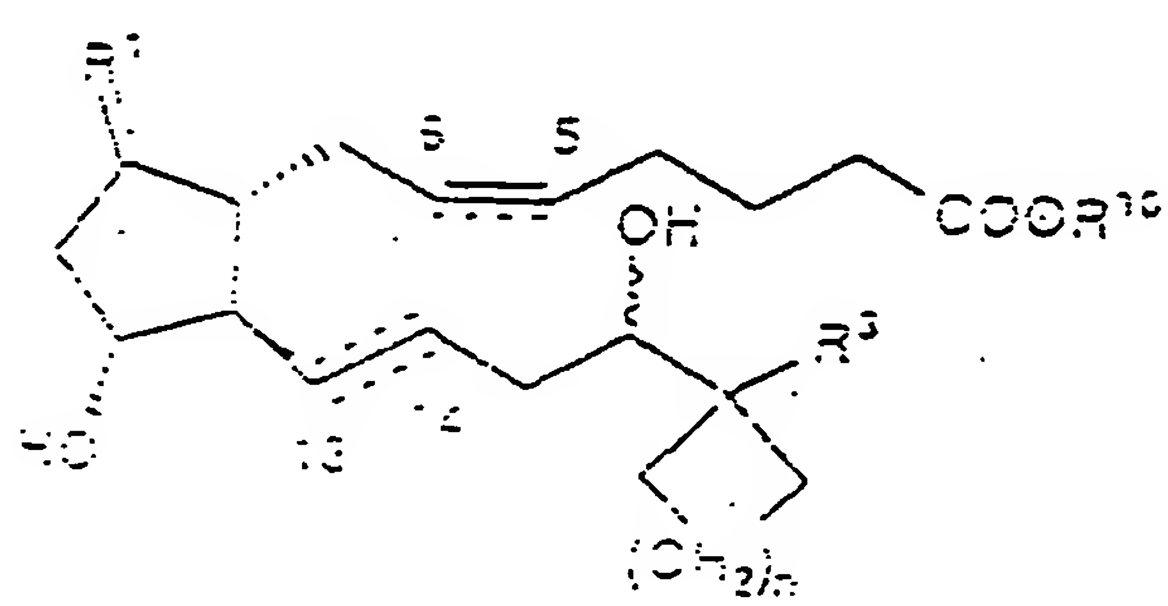
dans laquelle R^{21} est un atome d'hydrogène ou un groupe protecteur hydroxy qui peut être éliminé en milieu acide, et les autres symboles sont tels que définis dans la revendication 1 ou 9.

13. Procédé pour la préparation d'un composé promédicamenteux de la formule (IA) tel que défini dans la revendication 1, qui est de formule (IA2)



(IA-2)

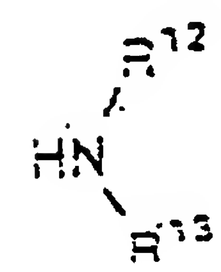
dans laquelle R^{23} est un alkoxy de C1 à 4 et les autres symboles sont tels que définis dans la revendication 1, lequel procédé comprend une alkylation-0 d'un composé de la formule (IA-3)



(IA-3)

dans laquelle tous les symboles sont tels que définis dans la revendication 1.

14. Procédé pour la préparation d'un composé promédicamenteux de la formule (IB) tel que défini dans la revendication 1, lequel procédé comprend une amidation d'un composé de formule (I-1) tel que défini dans la revendication 8 avec un composé de formule (IV)



(IV)

dans laquelle tous les symboles sont tels que définis dans la revendication 1.

15. Composition pharmaceutique qui comprend un composé de la formule (I) tel que défini dans la revendication 1, ou un sel non toxique de celui-ci ou un clathrate de cyclodextrine de celui-ci, ou un promédicament de celui-ci tel que défini dans la revendication 1, avec un support ou un enrobage.

16. Utilisation d'un composé de la formule (I) tel que défini dans la revendication 1, ou d'un sel non toxique de celui-ci, ou d'un clathrate de cyclodextrine de celui-ci, ou d'un promédicament de celui-ci tel que défini dans la revendication 1, dans la fabrication d'un médicament destiné à servir de liant du récepteur de sous-type EP_2.

17. Utilisation d'un composé de la formule (I) tel que défini dans la revendication 1, ou d'un sel non toxique de celui-ci ou d'un clathrate de cyclodextrine de celui-ci, ou d'un promédicament de celui-ci tel que défini dans la revendication 1, dans la fabrication d'un médicament pour la prévention et/ou le traitement des maladies immunes, de l'asthme, des malformations osseuses, de la déperdition neuronale, des détériorations hépatiques, des avortements, des naissances prématurées ou de la neuropathie rétinienne du glaucome.